IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC A/S and ANTON ANTON MAYR,	)	
Plaintiff,	)	
v.	)	C.A. No. 05-614 (SLR)
ACAMBIS INC. and ACAMBIS PLC,	)	REDACTED PUBLIC VERSION
Defendants.	)	

APPENDIX TO DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT ON CONVERSION CLAIM

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TABLE OF EXHIBITS

Exhibit	Description	Confidentiality Designation
1	Assignment Agreement November 6, 2002	CONFIDENTIAL
2	Expert report of Joseph Strauss	PUBLIC
3	Deposition of Anton Mayr September 21, 2006	CONFIDENTIAL
4	Deposition of Anton Mayr December 14, 2005	CONFIDENTIAL
5	"MVA Vaccination Against Smallpox," Stickl, Mayr et al. (1974)	PUBLIC
6	Section 7 Chemistry, Manufacturing and Control Information	CONFIDENTIAL
7	German Publication 2145 477, filed September 11, 1971, issued March 15, 1973	PUBLIC
8	Swiss Patent 568 392	PUBLIC
9	Deposition of Karl Heller February 16, 2006	CONFIDENTIAL
10	Gritz handwritten notes	CONFIDENTIAL
11	Deposition of Joseph Straus November 30, 2006	PUBLIC
12	Expert report of Dr. Winfried Tilmann	PUBLIC
13	Deposition of Peter Wulff September 21, 2006	CONFIDENTIAL
14	Moss letter to Mayr August 3, 2001	PUBLIC
15	NIH Lab Notebook	PUBLIC
16	ITC Response December 22, 2006	CONFIDENTIAL
17	Deposition of Peter S. Wulff February 9, 2006	CONFIDENTIAL

Exhibit	Description	Confidentiality Designation
18	“History of vaccine virus strain MVA”	CONFIDENTIAL
19	Notes from meeting with Anton Mayr April 28, 2005	CONFIDENTIAL
20	History of MVA 1974 Stock	CONFIDENTIAL
21	Deposition of Robert Drillien November 24, 2006	CONFIDENTIAL
22	Wulff email November 10, 2004	CONFIDENTIAL
23	Wulff email November 11, 2004	CONFIDENTIAL
24	Heyden letter to Berkley December 19, 2003	CONFIDENTIAL
25	IAVI Minutes February 3, 2004	CONFIDENTIAL
26	Mayr letter to Moss September 12, 2001	PUBLIC
27	Expert report of Ashley J. Stevens November 10, 2006	CONFIDENTIAL
28	Deposition of Ashley J. Stevens November 29, 2006	CONFIDENTIAL
29	Expert report of Louis P. Berneman November 10, 2006	CONFIDENTIAL
30	Deposition of Louis P. Berneman November 30, 2006	PUBLIC
31	Wulff email November 19, 1997	CONFIDENTIAL
32	Wulff email to Mowatt April/May 2002	PUBLIC
33	Wulff email August 10, 2001	CONFIDENTIAL
34	Deposition of David Einhorn November 30, 2006	CONFIDENTIAL
35	Moss letter to Mayr April 23, 2003	PUBLIC

Exhibit	Description	Confidentiality Designation
36	Deposition of Linda Gritz February 8, 2006	CONFIDENTIAL
37	Mazzara email to Butler March 12, 2002	CONFIDENTIAL
38	Wulff email September 8, 1999	CONFIDENTIAL
39	Wulff letter to Gritz April 9, 2002	PUBLIC
40	NIAID Biological Materials Transfer Agreement March 2003	CONFIDENTIAL
41	Mowatt letter to Wulff July 15, 2002	PUBLIC
42	Deposition of Bernard Moss August 28, 2006	CONFIDENTIAL
43	Request for Approval April 21, 1998	PUBLIC
44	Consulting Agreement March 30, 1998	PUBLIC
45	Gritz letters to Mayr 1995/1997	CONFIDENTIAL
46	Therion email to Cynthia Lee attaching word file of TBC-MVA	CONFIDENTIAL
47	Hartmann letter to Higgins June 5, 2002	CONFIDENTIAL
48	Electronic Request for Proposal RFP NIH-NIAID-DMID-03-44 (“RFP-1”)	PUBLIC
49	Mayr letters to Bennett June 1995	CONFIDENTIAL

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EXHIBIT 1

CONFIDENTIAL EXHIBIT

EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC A/S, Plaintiff, v. ACAMBIS INC. and ACAMBIS PLC, Defendants.	Civil Action No. 05-614 (SLR)

EXPERT REPORT AND/OR LEGAL OPINION OF

PROF. DR. DRES. H.C. JOSEPH STRAUS

I. INTRODUCTION

1. My name is Joseph Straus and I have been retained as a legal expert on German Law by Bavarian Nordic A/S ("BN") in connection with the above-referenced case in the United States District Court for the District of Delaware to study and provide opinion on certain issues relating to ownership to and/or intellectual property rights in certain Modified Vaccinia Virus Ankara ("MVA") strains and vaccines.

2. I understand that BN alleges conversion with respect to certain live biological material based on the use of BN's proprietary MVA-572 strain as the precursor for developing, producing and selling the MVA3000 vaccine product at issue in this investigation.

pp. 96-100 with numerous further references).

16. Under the German laws applicable to the facts of this case, a consequence of Article 5 III of the German Constitution (Grundgesetz – GG), in which the freedom of research is guaranteed and which, in the context of the issue at hand, also covers the right of exploitation and the respective exploitation activities, guaranteed under Articles 2, 12, 14 at Seq. GG (*Frieling*, Forschungstransfer: Wem gehören Forschungsergebnisse [Research Transfer: To Whom Belong Research Results], 1987 GRUR 407 at Seq., at 408), was that tangible as well as intangible results of the research work of a university professor belonged to the professor (*Frieling* 1987 GRUR 408 at seq.). It was up to the professor to take the decision whether and in which form to exploit own research results (*Ullrich*, Privatrechtsfragen der Forschungsförderung in der Bundesrepublik Deutschland [Civil Law Issues of Research Promotion in the Federal Republic of Germany], 1984, p. 290). In respect to inventions made by German university professors before February 7, 2002, the German Law on Employees Inventions in its Section 42 explicitly provided that "inventions made by professors, lecturers and scientific assistants, in their capacity as such, at universities and higher schools of science shall be free inventions." Since the facts at hand in this case all occurred before February 2, 2002, no need exists to examine the impact of the new law, neither in the context of tangible nor intellectual property.

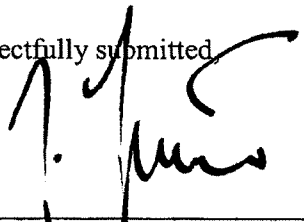
17. It is undisputed under the German law that tangible scientific research results, including naturally occurring substances such as bacteria or viruses, at least if they are limited in space, either by their own physical delimitations, or by being placed in a container or by some other artificial means, can be subject matter of tangible property rights (*Straus/Moufang*, op. cit., p. 96 and footnote 265 with further references). It is further undisputed that where the scientific and economic value of a research result is inseparably attached to the originally discovered or

39. Good faith depends on the circumstances. For example, there was no money transaction in connection with the shipment of this strain. In any event, Dr. Moss and the NIH were put on notice by Prof. Mayr and BN prior to the provision of the MVA-572 strain and/or its progeny to Acambis and certainly before any commercial use has been made of it.

40. Acambis was not and cannot have been in good faith as required by German law. For example, the MVA dated 9 September 2002 explicitly provides no warrant regarding freedom to operate and includes an indemnification clause to the benefit of the NIH. Acambis was put on notice by BN prior to receiving the MVA-572 virus strain regarding Bavarian Nordic's rights of Prof. Mayr's MVA viruses, and thus also regarding Prof. Mayr's rights to his man made MVA viruses, and certainly before any commercial use has been made of it. Acambis was further put on notice by the NIH of claims made by Bavarian Nordic and Prof. Mayr regarding legal rights to the MVA-572 virus strain prior to receipt of this particular strain and certainly before any commercial use has been made of it. Ignorance of the law is no defense to liability under the law.

41. Accordingly, Dr. Moss and/or NIH or Acambis cannot be considered bona fide purchasers and were therefore not free to use the MVA-572 strain and/or its progeny commercially.

Respectfully submitted,



Prof. Dr. Dres. h.c. Joseph Straus

EXHIBIT 3

CONFIDENTIAL EXHIBIT

EXHIBIT 4

CONFIDENTIAL EXHIBIT

EXHIBIT 5

Dtsch. med. Wschr. **99** (1974), 2386–2392

MVA Vaccination Against Smallpox

Clinical Tests with an Attenuated Live Vaccinia Virus Strain (MVA)

H. Stickl, V. Hochstein-Mintzel, A. Mayr, H. Ch. Huber, H. Schäfer and A. Holzner

Bavarian State Vaccination Institute and Institute for Microbiology and Infectious Diseases of Animals of the University of Munich

[see source for bilingual English summary]

Even today, a smallpox vaccination is still associated with a high risk. Post-vaccination complications, especially after an initial vaccination, are more common than with all other vaccinations apart from rabies vaccination.

For many years, various methods of reducing the complication rate with smallpox vaccinations have been proposed throughout the world. These include mainly simultaneous administration of γ-globulin or specific anti-vaccinia serum and so-called prevaccination using an inactive vaccine, mainly the vaccine antigen. The efficacy of these methods is disputed in the meantime with regard to adequate immune stimulus and from the standpoint of preventing complications.

For many years, an attenuated vaccinia virus has been under testing in animal experiments at the Bavarian State Vaccination Institute. This virus, which has been referred to in the course of these experiments as the “MVA” strain (modified vaccinia virus Ankara strain) has proven to be aviral in animal experiments. On the basis of findings on primates, it has been used to produce vaccine and has ultimately been used clinically on patients. The findings obtained in this regard are the subject matter of the present article.

Material and Methods

Vaccine

Virus strain. Vaccinia virus Ankara strain was attenuated by Mayr in continuous passages on cell cultures of embryonal chick fibroblasts. The attenuated virus was assigned the identification CVA-HFE. Its properties were characterized for the first time by Mayr and Munz [14] in the 371st passage. According to the results of experiments, the cultured virus differed significantly from the starting virus. The essential feature of the cultured virus was the great reduction in virulence in the animal experiment. Vaccinia virus strain CVA-FHE was taken over in the 516th passage by the Bavarian State Vaccination Institute and was continued on cell cultures of embryonal chick fibroblasts. The eggs used in these experiments came from the company TAD in Cuxhaven. According to certification of the supplier company, the chicken population is free of avian leukosis and other pathogenic microorganisms.

With regard to its use as a vaccine, vaccinia virus strain CVA-FHE has been subjective to comparative testing with vaccinia Elstree strain for virulence and immunogenicity [12, 15]. In these experiments, the low virulence of the CHA-HFE strain was confirmed, in particular its low neurovirulence. The immunogenicity of the CVA-HFE strain was weaker than that of the Elstree strain. At a suitable dose and with a suitable form of administration, however, formation of hemagglutination inhibiting and virus neutralizing antibodies could also be induced with the CVA-HFE strain. Monkeys of the *Macaca irus* and *Macaca mulatta* species were protected from the disease by immunization with the CVA-HFE strain after a test infection with *Variola vera*. In two preliminary studies, the effect of CVA-HFE strain on humans was tested [20, 23]. Intracutaneous injection of 0.1 mL virus suspension containing 2×10^5 infectious particles caused redness measuring approximately .2 × 2 cm and lasting for several days. There was no fever or any disturbance in general well-being. The conventional smallpox vaccination with Elstree strain Vaccinia virus, which was performed after 7 days, proceeded with the typical picture of a repeat vaccination.

Preparation of vaccine. Vaccine produced from the CVA-HFE strain was identified as MVA vaccine so the strain was renamed MVA strain Vaccinia virus. MVA stands for "modified Vaccinia virus Ankara strain." Material obtained from cell cultures was additionally identified as HFE, material from the chorioallantoic membrane received the additional CAM designation.

a) Production of the vaccine of the chorioallantoic membrane (MVA-CAM): The depressed chorioallantoic membrane of leukosis-free chick eggs incubated for 10 days was inoculated with 1000 infectious virus unit in a volume of 0.1 mL. After incubating the eggs for 48 hours at 37°C, the membranes were harvested, washed again in phosphate buffer NaCl solution and deep frozen. After thawing, the membranes were placed in a 10-fold amount (rate/volume) of McIlvaine buffer and homogenized with 10% Freon®. After centrifugation for 10 minutes at 800 g, the supernatant was sedimented in 1 hour at 10,000 g, the sedimented was suspended in the starting amount with McIlvaine buffer and centrifuged a second time at a high speed. The second sediment was the starting material for preparation of the vaccine. After suspension in McIlvaine buffer, the virus content was ascertained and adjusted to 4×10^6 infectious units per milliliter for appropriate dilution. The virus suspension was stabilized by adding 1% human serum albumin and freeze-dried in 0.5 mL portions.

b) Production of the vaccine from the cell culture: The cell cultures for replication of the virus were prepared from 12-day old chick embryos of leukosis-free eggs according to the standard technique. The growth medium contained yeast extract, lactalbumin and 10% calf serum. After 48 hours, the cell growth was complete and was washed with phosphate buffered saline solution and then inoculated. The virus concentration in the inoculation medium was 10^6 infectious units per milliliter. After incubating for 72 hours at 37°C, the medium was poured off, the cell growth was washed again and extracted with 20.0 mL McIlvaine buffer and then frozen. After thawing the dishes, further processing of the vaccine was performed as in the production of the virus from infected chorioallantoic membrane.

Shipping the vaccine. The vaccine was shipped at no cost on written request to clinics and to private doctors' practices. An original package contained 0.5 mL freeze-dried vaccine, enough for two vaccinations.

So far approximately 12,500 vials of MVA vaccine have been shipped. This corresponds to approximately 25,000 vaccine doses.

Use of the vaccine

According to experience in the pilot studies, the vaccine should be injected intracutaneously in a dose of 0.2 mL on the side surface of the forearm. Phosphate-buffered saline solution is used as the solvent for the dry vaccine solids. The MVA vaccination is performed as a "step vaccination," i.e., the vaccination with MVA vaccine is to be followed by a conventional smallpox vaccination in any case. The success of the conventional vaccination must be checked as usual by re-testing 8 days after the vaccination based on the traditional evaluation criteria: this was done because the requirements of the valid statutory vaccination law are not met by vaccination exclusively with the MVA strain.

Analysis of the vaccination results

Reporting forms. Each physician received a reporting form together with the vaccine with instructions to use the reporting form to record all observations that might be important for an evaluation of the safety and efficacy of this vaccine.

The reporting forms are divided into three sections. The first section contains information about the patient receiving the vaccination, the most important of which is the age at vaccination, divided (according to the conventional limit for being "above age" for smallpox vaccination) into a group with an age of more than three years and a group with an average of less than three years. The vaccination status was either initial vaccination or repeat vaccination. The question of a vaccination interval was not addressed because in this study value was placed mainly on the observation of initial vaccinations anyway. The vaccination indications were summarized according to their empirical frequency and also according to relevance for the evaluation of the safety of the method tested.

The second section of the reporting form contains questions about the observations after MVA vaccination. The local reaction should be described immediately after the injection and then 2 and 7 days after the injection.

The questions about possible disturbances in general well-being are deliberately formulated in an undifferentiated manner because our experience indicates that these questions are answered primarily by the layman.

The third section of the reporting form contains questions about the observations of the main cutaneous vaccination, differentiated essentially according to the local vaccination reaction and the systemic vaccination reaction. The questions about the local vaccination reaction differ from our usual classification according to "vesicular reaction," "pustular reaction," "nodular reaction," i.e., a, b and c reactions, because this classification is neither logical nor does it allow differentiation without any doubt among the various types of reactions. However, the reaction types proposed on the questionnaire:

Vesicles or pustules	without scab
Vesicles or pustules	with scab
Nodules (or infiltrate)	without scab
Nodules (or infiltrate)	with scab

should allow a satisfactory classification. In addition, this should largely objectify the difficult decision between initial vaccination and repeat vaccination. Only pustules without a scab or vesicles without a scab should be considered typical initial vaccination reactions in the analysis. In addition, the reaction types selected allow a classification into the reaction types proposed by the World Health Organization, i.e., "positive" ("major reaction"), "questionable" ("equivocal reaction") and negative.

The questions about concomitant symptoms of the vaccination are also very general in this section to facilitate the decision on the part of the evaluating physician as much as possible and thereby arrive at a clear conclusion.

Analysis[1]. Instead of the individual reporting forms, in many case a lump sum report of the vaccination results was given. Many of these reports contained only reports about the vaccination being fever-free and without complications. There was no analysis of these lump sum empirical reports. Nor were the individual questionnaires analyzed if they were not filled out adequately.

Seven thousand ninety-eight forms were available for statistical analysis. Any inadequate or unclear information was not evaluated. The information from each individual reporting form was processed by computer using punched cards.

The questions to be answered have been summarized in the following catalog of questions:

Question 1: On the basis of which indications was the MVA step vaccination performed?

CNS diseases	blood disease
Skin diseases, allergy	concerned parents
Chronic disease	other reason
Intestinal disease	no particular indications

[1] We want to express our appreciation to Dr. Drausnick of the Bavarian State Ministry of the Interior and the Bavarian Statistical State Office for assistance in performing the statistical analyses.

Question 2: In how many vaccinated patients was any one of the following reactions observed at the vaccination site 24 to 48 hours or 5 to 7 days after the MVA vaccination (first vaccination stage)?

No reaction
Redness up to 10 mm with infiltrate
Redness up to 10 mm without infiltrate
Redness 10–20 mm with infiltrate
Redness 10–20 mm without infiltrate
Redness more than 20 mm with infiltrate
Redness more than 20 mm without infiltrate

Question 3: How many vaccinated patients have experienced concomitant symptoms (fever more than 38°C and/or disturbance in general well-being) after the MVA vaccination (first vaccination stage)?

Question 4: How many vaccinated patients have developed any one of the following evaluations of local findings of the main epicutaneous vaccination (second vaccination stage) on the 7th day after vaccination?

Vesicles or pustules	without scabbing
Vesicles or pustules	with scabbing
Infiltrate or nodules	without scabbing
Infiltrate or nodules	with scabbing
Negative local findings	

Question 5: In how many cases did concomitant symptoms develop after the epicutaneous main vaccination (second vaccination stage) and which type of concomitant symptoms were they?

Table 1. Leading indications for MVA step vaccination.
Number of cases observed: 3850

Central venous disease	3.1%	Blood diseases	0.25%
Skin disease, allergy	8.4%	Concerned parents	23.0%
Chronic disease	2.0%	Other reason	13.9%
Intestinal disease	0.5%	No particular indication	48.4%
No information	0.4%		

Results

The results are summarized in Tables 1 through 5. The different total number of observations for the individual questions is due to the fact that many questions were not answered on all questionnaires.

So far a total of 7098 first vaccinated patients have been covered by the study. Five thousand six hundred ninety-one were less than 3 years old and 1407 were more than 3 years old.

Discussion

The conventional attempts to improve the tolerability of vaccinations have previously taken into account the condition of the vaccinated patient prior to vaccination and attempted to attenuate the systemic response to epicutaneous prophylactic vaccination through various vaccination

methods in the hopes of thereby avoiding vaccination complications.

However, with our good epidemiological situation, smallpox vaccination is aimed directly at a smallpox infection only in extremely rare cases, so the goal of the initial vaccination is to create a basal vaccination immunity so that in the serious case a low-risk repeat vaccination can be administered. In Germany, an infant or toddler will hardly come in contact with *Variola vera*. Previous experience has shown that exposure occurs in later years, however, this means that we are "vaccinating against the vaccination" [23, 24].

Attempts with vaccine antigen have not proven adequately successful because vaccine antigen merely induces a cellular allergy. The vaccine antigen is a fully virulent vaccinia virus that has been inactivated by treatment with formaldehyde. This destroys mainly the nucleoproteins. The proteins are partially denatured and the lipoproteins of the shell are preserved. However, the latter is the actual allergen. The significance of this component of the vaccinia virus is low in terms of immunization. The vaccine antigen is therefore regarded as more or less ineffective in Anglo-American and Swiss literature.

An attempt to burden an adoptive immunity induced by vaccine antigen by adding vaccinia virus or variola virus has not been successful in detecting a protective effect of the vaccine antigen [11, 19].

The efficacy of the preparation as an allergen is illustrated by allergic reactions (rash, vaccination ulcer) in an incidence of 5 to 8% in the subsequent vaccination using the original vaccinia virus.

Attenuated vaccinia virus MVA, however, has an intact nucleoprotein component. The formation of hemagglutinin has been reduced by culturing in cell passages. Only with repeated injections of MVA have low titers of hemagglutination inhibiting antibodies in the serum been detected in experimental animals.

Nevertheless, MVA is capable of building up a true anti-infectious immunity without any greater infectious allergic vaccination reaction.

Experience since the introduction of the smallpox vaccination has shown that cerebral complications almost never occur after a repeat vaccination (incidence lower than 1:2,000,000). All observed cases have so far involved such atypical findings that it is reasonable to have serious doubts that repeat vaccination encephalitis exists at all [10].

For the MVA stepwise vaccination, this means that—even in the absence of hemagglutination inhibiting antibodies—no CNS disorders need be expected if a repeat vaccination reaction is induced in a second vaccination using fully virulent vaccinia virus.

Therefore, the goal of this investigation was to ascertain to what extent the initial vaccination stage with MVA would furnish the person receiving the initial vaccination with a basal vaccination immunity, i.e., giving this person the responses of a person receiving a repeat vaccination.

The simplest proof of basal vaccination immunity is vaccination with a virulent vaccinia virus and subsequent evaluation of the vaccination reaction.

The clinical signs after a prophylactic smallpox vaccination have been well known for a long time and have been described in detail in the literature. A summary review was given recently by Herrlich [10] in the Handbook for Prophylactic Vaccinations.

We differentiate the local reaction at the vaccination site and the general systemic vaccination reaction. The local vaccination reaction shows two characteristic manifestations: the initial vaccination reaction and the repeat vaccination reaction. The initial vaccination response leads over the course of several days to formation of a pustule by way of a papule and vesicle stage. The pustule reaction has reached its peak on the 7th day after the vaccination. Then the stage of scabbing begins. The local reaction ends with the scab falling away and formation of a scar.

The repeat vaccination reaction is a reliable sign that the body has already had an immunological encounter with the virus, so this is an important criterion for the immune status and the success of previous vaccinations.

The most important difference between the initial vaccination reaction and the repeat vaccination reaction is the accelerated course. Although the repeat vaccination reaction might pass through the same morphological stages of the initial reaction, the individual stages are shortened in time, however. An important criterion that is important in evaluating the vaccination reaction on the seventh day after the vaccination is being morphological manifestation of the vaccination pustule:

Whereas the initial vaccination reaction is to form a taut pustule without any scabbing at all, the repeat vaccination reaction on the same day develops more or less completely scabbing of the pustule.

The systemic reactions are generally less pronounced in repeat vaccinations than in initial vaccinations.

The transition between the normal general vaccination reaction, which accompanies almost every smallpox vaccination, and the vaccination complication is fluid. It is often difficult to find the causal relationship with the prior smallpox vaccination in the case of uncharacteristic disorders in general well-being.

General symptoms that are often mentioned following a smallpox vaccination include: fever, fatigue, joint pain, headaches, swelling and painful local lymph nodes, transient exanthem, isolated secondary pustules or secondary efflorescences. The relative frequency with which such symptoms occur after an initial vaccination and a repeat vaccination cannot be ascertained because they are tolerated as "normal" vaccination reactions and do not get included in statistics. The observations on smaller vaccination groups with respect to such manifestations are doubtfully representative especially since they are usually based on clear-cut vaccination subjects.

In addition to these manifestations which are considered to be an abnormal vaccination response only due to their severity, there are specific vaccination complications which include, first, the disease syndromes that are recognizable as vaccination lesions of the outer integument (vaccinia generalisata, eczema vaccinatum, vaccinia ulcerosa) and secondly, the disorders of the central nervous system known collectively as post-vaccination encephalopathy and encephalitis.

The third category includes all complications not specifically caused by the vaccination disorder but clearly occurring as a result of the vaccinia infection and the predisposition thereby created. Stickl [18, 21] and other authors have pointed out the importance of these diseases in

evaluating vaccination damage. These are attributed mainly to a change in the body's reaction with lowered resistance to bacterial infections.

The evaluation of the incidence of individual complications is subject to great fluctuations. These discrepancies in the evaluation have been the subject matter of scientific discussion at all times without being able to achieve a clear-cut elucidation so far.

Safety

The information about MVA vaccination is based on 7098 initial vaccination recipients. They were divided into those less than 3 years of age and those more than 3 years of age. The second group was formed because according to the consensus so far, the third year of life is the cut-off limit for "being above age" for the first vaccination. After the third year of life, in the opinion of various authors, the incidence of cerebral complications is greater than that in younger vaccination patients [1–4, 6–9, 16].

The local reaction after initial MVA immunization is manifested as an approximately circular area of redness at the intracutaneous vaccination site with or without minor infiltration. After 24 to 48 hours, the area of redness reaches a diameter of up to 10 mm (in 54.9% of the cases), of 10–20 mm (31.45%) or in a few cases (6.4%) more than 20 mm. In 367 vaccination patients (7.25%) the local response was negative (Table 2). This may be an inadequate response of the vaccination patient but it may also be attributed to the injection of the vaccine being too deep, inadvertently subcutaneous. With a subcutaneous injection, no local reaction occurs with the dose of infectious virus specified for MVA. Nevertheless, this form of administration is without influence on the results of the reaction of the second vaccination stage.

Table 2. Local reaction after MVA vaccination (first vaccination stage)
24–48 hours and 5–7 days after vaccination (p.v.).

	24–48 hours p.v. (number of cases: 5065)	5–7 days p.v. (number of cases: 5308)
No reaction	7.25%	9.17%
Redness up to 10 mm	54.90%	75.45%
Redness 10–20 mm	31.45%	14.05%
Redness more than 20 mm	6.40%	1.53%

Seven days after the MVA vaccination, the local findings according to type and extent are weaker than after 24 to 48 hours. The distribution among the categories "negative," "up to 10 mm," "10–20 mm" and "more than 20 mm" changes on the fifth to seventh day in favor of the weaker reactions, namely the negative reactions increase from 7.25% to 9.17%, the reactions with a diameter of up to 10 mm increases from 56.61% to 75.45%. However, the reactions with a diameter of 10 to 20 mm decreases from 30.61% to 14.05% and those with a diameter of more than 20 mm decrease from 4.82% to 1.53%.

It seems especially worth mentioning except for redness and infiltration, no more extensive reactions at the vaccination site were observed: no vesicles or pustules and no ulcerations. Not even minor scabbing of the injection site has been reported. This is important because a classical cutaneous vaccination reaction can also be expected with the low local infection dose of 2×10^5 infectious virus particles when using conventional Vaccinia strains. A review article by Dostal [5] shows that a conventional strain with a virus content of approximately 10^6 infectious particles/mL, corresponding to the virus content of MVA vaccine, causes the vaccination to "take," i.e., causes a pustule reaction, in 50% of all first vaccinations. We can conclude from this comparison that the skin virulence of the MVA strain is greatly reduced in humans in comparison with conventional vaccinia strains. The reduced skin virulence has also been demonstrated in animal experiments by Mayr and Munz [14] and by Hochstein-Mintzel et al. [12] on the rabbit and monkey.

The local reaction after MVA vaccination has thus proven to be without a doubt milder than the reaction after conventional prophylactic vaccination. Consequently, none of the complications that are expected with prophylactic smallpox vaccinations involving the skin as an organ, including vaccinia generalisata and eczema vaccinatum, occur with MVA vaccination. Furthermore, MVA virus can be expected to cause no complications that are secondarily attributable to destruction of epidermal structures. We should think here primarily of post-vaccination encephalitis, the development of which is to be explained presumably in conjunction with the phylogenetic bridges between the skin and brain and the antigen relationships to be expected with this [22].

In most cases no general reaction has occurred after MVA vaccination. Only 2.28% of the patients vaccinated have developed fever and 4.11% reported a disturbance in general well-being. With the incidence with which fever and a disturbance in general well-being occur in children normally anyway, not all the observed cases will have to be causally attributable to the vaccination. Even if all observed febrile courses are attributed to the MVA vaccination, a febrile vaccination response of only 2.28% of all children receiving vaccinations may be considered minor (Table 3).

Table 3. Concomitant symptoms after MVA vaccination (first vaccination stage).
Number of cases observed: 7098.

Fever above 38°C	2.28%
Disturbance in general well-being	4.11%

The tolerability of the vaccination method is thus documented by Tables 2 and 3. In addition to the 7098 individually analyzed cases, there are numerous general reports of vaccinations proceeding without any complications. In view of the fact that any serious complication would have to be reported immediately, this greatly increases the empirical relevance of our study.

Efficacy

The classical proof of efficacy of prophylactic vaccination is an increase in hemagglutination-inhibiting or virus neutralizing antibodies, but this proof cannot be obtained for a single MVA vaccination alone. This had already been demonstrated in animal experiments [12] and in

humans [20]. An increase in the level of antibodies can be detected only by administering two MVA vaccinations with high virus doses. However, antiviral immunity is determined not exclusively by humoral defense mechanisms but also by cellular defense mechanisms, the details of which are not understood.

This can be demonstrated by indirect evidence, namely when an anti-infectious immunity is observed clinically but no serologic antibodies can be detected. In animal experiments, it has been observed that after MVA vaccination, there has been increased resistance to the stress or infections with variola virus although there was no serological evidence of antibodies in these animals [13].

The classical proof of the changes in tissue reactivity of a person having vaccinia immunity is the accelerated course of a vaccination reaction on receiving a repeat vaccination. The definitely different manifestations of initial vaccination reaction and repeat vaccination reaction have already been pointed out in the discussion.

In our field study, the cutaneous vaccination reaction type after a conventional smallpox vaccination became the parameter of efficacy of an MVA vaccination: if the cutaneous vaccination is accelerated when administered after an MVA vaccination, i.e., if it proceeds as a repeat vaccination reaction, then the MVA vaccination must have induced an immunization (sensitization). If the conventional cutaneous smallpox vaccination after MVA vaccination proceeds without any signs of influence, then the MVA vaccination would be of no effect.

Proof of the immunogenic efficacy of MVA in animal experiments had already been obtained prior to the clinical trial. Animals of various species were to be immunized against an infectious burden with vaccinia virus as well as against an infectious burden with variola virus. The efficacy was essentially a question of immunization dose, whereby assuming the same dose the Elstree strain was more effective than the MVA strain [12].

Table 4 summarizes the observations on humans regarding the cutaneous vaccination reaction following MVA vaccination. The classification criteria were selected so that they did not have to allow a clear differentiation of reaction types. At the same time, they should allow a classification of the vaccination reactions according to the classification proposal of the World Health Organization and ultimately should help in objectifying the question of the evaluation as "first" or "repeat vaccination reaction."

Table 4. Local reaction after epicutaneous vaccination with dermovirus Elstree strain
(second vaccination stage) on day 7 after vaccination.
Number of cases observed: 6894.

Vesicles or pustules without scabbing	18.10%
Vesicles or pustules with scabbing	47.65%
Infiltrate or nodules with scabbing	18.51%
Infiltrate or nodules without scabbing	8.69%
Negative local findings	7.05%

Assuming that the classical initial vaccination reaction is characterized by a pustule without scabbing on the seventh day after vaccination, then Table 4 shows that this requirement is met in only 18.1% of the cases. The reported objective findings at the vaccination site thus yielded only 18.1% traditional initial vaccination reactions although 100% was expected because there were exclusively initial vaccination patients. The percentage of negative reactions (7%) ascertained in this group is unusually high for patients receiving an initial vaccination. The observed percentage is reminiscent of numbers that would be expected for repeat vaccinations.

The difficulty with the smallpox vaccination "taking" after an MVA vaccination has also been expressed in numerous reports and inquiries from colleagues by telephone.

If we assume the nodule reaction without scabbing in the sense of the WHO classification to be a reaction with questionable vaccination success, this yields the following distribution of reactions:

Vaccinations total	6894 (100%)
of these, successful	
in the sense of an initial vaccination reaction	1248 (18.1%)
in the sense of a repeat vaccination reaction	4561 (66.16%)
positive (major reaction)	5809 (84.26%)
questionable (equivocal reaction)	599 (8.69%)
negative	486 (7.05%)

The distribution of reaction types according to main cutaneous vaccination is approximately the same with all types of local MVA reaction. Even with negative local findings after MVA vaccination, initial vaccination reactions after cutaneous main vaccination are no more common than after strong local reactions. This suggests that intracutaneous administration and local signs of irritation of the skin are not a condition for successful immunization.

Animal experiments have also shown that immunization against pox is possible, bypassing the skin. Rabbits and monkeys have been successfully immunized against vaccinia and variola by administering the vaccine intramuscularly [13]. These experimental findings and the results of clinical testing might allow the conclusion that the interfering local vaccination reaction should be eliminated in MVA vaccination and the vaccine should be administered subcutaneously, intramuscularly, orally or in the form of an aerosol.

The efficacy of the MVA vaccination in addition to the local vaccination reaction, the incidence of fever and other disturbances in general well-being after cutaneous main vaccination was interpreted as the second criterion. Reliable numbers regarding the incidence of fever with conventional initial vaccination of healthy children are difficult to obtain. In general terms, however, it can be concluded that the so-called vaccination fever is a "normal" concomitant reaction to a smallpox vaccination. In our study, fever was reported in 18.39% of 5982 cases analyzed. The majority (58.87%) of the vaccinated children having a febrile reaction course, broken down according to extent of fever and duration of fever, had a temperature rise of only up to 38.5°C for less than 2 days. A greater increase in temperature for a shorter or longer period of time (22.49% and 11.24% for less than 2 days and more than 2 days, respectively) were far less common; likewise the longer persistence of lower temperatures (7.40%).

The other concomitant systems after cutaneous main vaccination were of a harmless nature and are not observed in this frequency with repeat vaccinations (Table 5).

Table 5. Incidence of concomitant symptoms after epicutaneous vaccination with

Elstree strain dermovirus (second vaccination stage). Number of cases observed: 5691.

Nausea/vomiting	0.78%
Cerebral symptoms	– *
Febrile convulsion	– *
Rash	0.78%
Lymph node swelling	3.82%
"Other"	2.60%

*In an earlier publication [17], three neurological symptoms were listed. A follow-up of these cases has revealed that there was no correlation with the smallpox vaccination.

No CNS complications of the vaccination were observed. However, since the number of cases observed here is too small, a final conclusion regarding the incidence of encephalitis cannot yet be made.

The morphological course of the MVA stepwise vaccination with "nodule reaction," accelerated scabbing reaction shows that the second vaccination stage usually proceeds as a repeat vaccination reaction in the essential biological immunological criteria. Therefore, the contraindications of an MVA stepwise vaccination would be equivalent to those for a repeat vaccination.

One difficulty with the MVA stepwise vaccination should be pointed out: it is often impossible to clarify whether a bland accelerated scabbing reaction can be interpreted as a sign of adequate vaccination success. In case of doubt, a revaccination should always be performed after a few months or the success of the vaccination should be confirmed by the neutralization test.

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EXHIBIT 6

CONFIDENTIAL EXHIBIT

EXHIBIT 7

(51) Int. Cl.: A 61 k, 23/00

FEDERAL REPUBLIC OF GERMANY
GERMAN PATENT OFFICE

(52) German Cl.: 30 h, 6

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(54) Title: Method for Small Pox Vaccination

(61) Amendment to: -
(62) Division of: -
(71) Applicant: Free State of Bavaria, represented by the Bavarian State Interior Ministry, 8000 Munich

Representative according to § 16 PatG (German Patent Act)

(72) Named as inventors: Stickl, Helmut, Prof. Dr. med., 8033 Krailling
Mayr, Anton, Prof. Dr., 8000 Munich

cf. Bur.-L. 37/73

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Free State of Bavaria, represented by
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8 Munich 22, Odeonsplatz 3

Method for Small Pox Vaccination

The invention relates to a method for small pox vaccination.

In the previously common vaccination against small pox, using a strongly reactogenic vaccine stem and using the epicutaneous scarification with the insertion of the virus, at a certain temporary progression the formation of an inoculation pustule occurs. The latter is an expression of an infectious-allergic occurrence, with cellular-allergic reactions being focused on.

It has been a known fact for a long period of time that the reactogenity of a vaccination is not identical to its immunogenity: this means that strong vaccine-reactions not necessarily lead to a strong protection from infection against the sickening variola virus. In the most recent years, this knowledge was the reason for the introduction of the lesser reactogenic vaccine stem elstree, however also using epicutaneous scarification.

The disadvantage of this type of small pox vaccination include that in many cases it leads to EBO-modifications, in particular when an additional sensitivity occurs. The cause for this are phylo-genetically caused, functional bridges between the central nervous system and the skin.

For this reason, it seems that the requirement to cause a cutaneous pustule reaction in the small pox vaccination and simultaneously the desire to perform a risk-free vaccination cannot be accomplished simultaneously; because as long as the immuno-allergic reaction on the skin is required to occur in this manner, it cannot be avoided that neuro-allergic side reactions in the central nervous system occur as well. - 2 -

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Therefore, attempts have been made to work with so-called "attenuated vaccines." All such experiments assumed that a normal vaccinia - virus is grown via 20 to 50 passages on the chorionic – allantoinic membrane and subsequently is used for the vaccination in a relatively high concentration. The passage of the vaccine virus via the chicken embryo has indeed led to a selection of non-uniform vaccine stems so that after several cultures an essentially genetically uniform vaccine stem can be yielded. Furthermore, in these vaccines a reduction of the reactogenity occured, i.e the local vaccination reaction was milder and fewer vaccination fevers occured; the viremia rate could also be significantly reduced with such vaccines. However, even using this method, the pustulous vaccination reaction was not waived. Therefore, vaccinations with these vaccine stems also resulted in central-nervous system complications with the same expected frequency as following immunizations with conventional vaccines.

Finally, it has also been attempted to vaccinate with normal vaccines either subcutaneously, which resulted in up to 60 % swellings in the subcutaneous tissue, or intracutaneously, which again resulted in pustules, this time with tissue necroses.

In contrast thereto, the invention is based on the knowledge that, in order to avoid the disadvantages of all previously known vaccination methods against small pox, it is deciding to use a vaccine causing no cutaneous vaccination reactions, such as a formulation of a vaccination pustule.

According to the invention this is attained in a method for a vaccination against small pox such that the vaccination occurs intracutaneously with an attenuated, modified vaccine. Advantageously, the vaccinia-virus Ankara is used, here, which is bread in more than 500 passages in chicken fibroblast-cells so that a modified, genetically uniform vaccinia virus is provided, which is weakened in its reactogenity and virulence by said cell passages. Here, 1 ccm of the finished vaccine contains, in a cleaned lyophilized form, approximately 10^7 virus particles; 0.1 ccm up to a maximum of 0.2 ccm are injected intracutaneously. This way, a more precise dosage is possible than in the previously known vaccination methods. Additionally, the control of the vaccination process is permitted such that at the site of the injection a reddening, slight swelling with a diameter of 4 x 8 mm and sometimes itching occurs as well; however, in no case any pustule vaccination reaction occurs. A humoral (serum connected) and tissue sensitivity (allergy) in a clinically significant form does not appear, however a cellular immunity can be proven, which prevents the spreading and multiplication in the tissue.

When using the method according to the invention the vaccination reaction progresses without any fever or other effects influencing the general appearances, in contrast to the previously known vaccination methods, in which sometimes symptoms such as vaccination fever, vaccination ulcers (abscess), vaccination exanthema (rash) occur and even inflammation of brain cells, which always result in lasting, if not fatal damage.

8 days after the injection the reddening and the swelling vanish, however, initially at the injection site a small yellow-brownish tubercle remains visible, which can also be felt, however, it vanishes no later than 21 days later.

Another essential advantage of the method according to the invention is to be seen in the possibility to achieve a basic vaccinal immunity, which prevents to fall ill to the above-mentioned complications of the vaccination methods known. When this basic immunity is given all other vaccinations according to conventional methods against small pox can no longer lead to the inflammation of brain cells. The method according to the invention is therefore suitable to perform the vaccination without any danger in cases, in which previously, due to age or sickness, contraindications against vaccinations were unavoidable.

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Bavarian State Interior Ministry - 5 -

Attachment

to the letter of the BAVARIAN STATE INTERIOR MINISTRY, dated November 15, 1971, No. P 4 – 5173/1 – 671

Entered on 11/26/71 *Filing: 12/2/71*

Amended Claims
for the Application P 21 45 477.3

1. A vaccine for the intracutaneous vaccination against small pox, **characterized in that** the vaccine comprises attenuated, modified vaccinia viruses.

2. A vaccine according to claim 1, **characterized in that** the vaccine is formed by using the vaccinia virus Ankara, which is bread in more than 500 passages in chicken – fibroblast cells.

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(51) Int. Cl.: A 61 k, 23/60

BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

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(33) Land: —

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(54) Bezeichnung: Verfahren zur Pockenschutzimpfung

(61) Zusatz zu: —

(62) Ausscheidung aus: —

(71) Anmelder: Freistaat Bayern, vertreten durch Bayer. Staatsministerium des Innern, 8000 München

Vertreter gem. § 16 PatG: —

(72) Als Erfinder benannt: Stickl, Helmut, Prof. Dr. med., 8033 Krailling

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Verfahren zur Pockenschutzimpfung

Die Erfindung betrifft ein Verfahren zur Pockenschutzimpfung.

Bei der bisher üblichen Impfung gegen Pocken unter Verwendung eines stark reaktogenen Impfstammes und unter Anwendung der epicutanen Skarifikation bei Insertion des Virus kommt es in bestimmtem zeitlichem Ablauf zur Ausbildung einer Impfpustel. Letztere ist Ausdruck eines infektiös-allergischen Geschehens, wobei zellulär-allergische Reaktionen im Vordergrund stehen.

Es ist eine schon seit längerer Zeit bekannte Tatsache, daß die Reaktogenität einer Impfung nicht identisch ist mit deren Immunogenität: dies bedeutet, daß starke Impfreaktionen nicht auch zu einem starken Infektionsschutz gegenüber dem krankmachenden Variola-Virus führen müssen. Diese Erkenntnis war in den letzten Jahren Grund für die Einführung des weniger reaktogenen Impfstammes Elstree, allerdings auch unter Anwendung der epicutanen Skarifikation.

Der Nachteil dieser Art der Pockenschutzimpfung besteht darin, daß sie in nicht seltenen Fällen, besonders wenn es zu einer zusätzlichen Sensibilisierung gekommen ist, zu EEG-Veränderungen führt. Ursache hierfür sind phylogenetisch angelegte funktionelle Brücken zwischen Zentralnervensystem und Haut.

Aus diesem Grunde erscheinen die Forderungen, bei der Pockenimpfung eine cutane Pustelreaktion herbeizuführen und gleichzeitig eine risikofreie Impfung durchführen zu wollen, miteinander nicht vereinbar; denn so lange eine

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so ausgeprägte immun-allergische Reaktion an der Haut erzwungen wird, kann nicht verhindert werden, daß nicht auch neuroallergische Begleitreaktionen am Zentralnervensystem auftreten.

Man hat daher versucht, mit sogenannten "Attenuierten Impfstoffen" zu arbeiten. Alle diese Versuche gingen davon aus, daß normales Vaccinia-Virus über 20 bis 50 Passagen auf der Chorion-allantoismembran gezüchtet wurde und dann in einer relativ hohen Konzentration bei der Impfung zur Anwendung kam. Die Passage des Impfvirus über den Hühner-Embryo führte in der Tat zu einer Selektion nicht einheitlicher Impfstämme, so daß nach mehreren Kulturen ein genetisch im wesentlichen einheitlicher Impfstamm gewonnen werden konnte. Ferner kam es bei diesen Impfstoffen zu einem Rückgang der Reaktogenität, d.h., daß die lokale Impfreaktion milder war und weniger Impffieber auftrat; auch die Virämierate bei Impfung mit solchen Impfstoffen ist deutlich reduziert. Aber auch bei dieser Methode wurde nicht auf die pustulöse Impfreaktion verzichtet. Dementsprechend waren bei Impfungen mit diesen Impfstämmen ebenfalls zentral-nervöse Komplikationen mit fast der gleichen Erwartungsfrequenz wie nach Impfung mit konventionellen Impfstoffen eingetreten.

Schließlich hat man auch schon versucht, mit normalem Impfstoff entweder subcutan zu impfen - das ergab bis zu 60 % Schwellungen im Unterhautgewebe -, oder aber intracutan - das ergab ebenfalls wieder Pusteln und zwar mit Gewebenekrosen.

Demgegenüber geht die Erfindung von der Erkenntnis aus, daß es - um die Nachteile aller bisher bekannten Pockenschutzimpfverfahren zu vermeiden - darauf ankommt, einen Impfstoff zu verwenden, bei dem keine cutane Impfreaktion wie Bildung einer Impfpustel auftritt.

Gemäß der Erfindung wird dies durch ein Verfahren zur Pockenschutzimpfung erreicht, bei dem intracutan mit attenuiertem, modifiziertem Impfstoff geimpft wird. Vorteilhafterweise wird dazu das Vaccinia-Virus Ankara verwendet, das in über 500 Passagen in Hühner-Fibroblasten-Zellen gezüchtet ist, so daß ein modifiziertes, genetisch einheitliches, in seiner Reaktogenität und Virulenz durch die Zellpassagen abgeschwächtes Vaccinia-Virus vorliegt. Dabei enthalten 1 ccm des Fertigimpfstoffes, in gereinigter lyophilisierter Form, etwa 10^7 Viruspartikel; 0,1 ccm bis maximal 0,2 ccm werden intracutan injiziert. Damit ist eine genauere Dosierung als bei den bisher bekannten Impfverfahren möglich. Außerdem ist aber eine Kontrolle des Impfverlaufes dadurch gegeben, daß sich an Ort und Stelle der Injektion Rötung, leichte Schwellung mit Durchmesser von 4 x 8 mm und manchmal auch Juckreiz zeigen; es kommt aber auf keinen Fall zu einer pustulösen Impfreaktion. Eine humorale (serumgebundene) und gewebliche Sensibilisierung (Allergie) in klinisch nennenswerter Form tritt also nicht ein, jedoch ist eine celluläre Immunität, die eine Ausbreitung und Vermehrung im Gewebe verhindert, nachweisbar.

Bei Anwendung des erfindungsgemäßen Verfahrens läuft die Impfreaktion ohne Fieber und beeinträchtigende andere Allgemeinerscheinungen ab, im Gegensatz zu den bisher bekannten Impfverfahren, bei denen zuweilen Krankheitserscheinungen wie Impffieber, Impf-Ulcus (Geschwür), Impf-Exanthem (Ausschlag) auftreten und sogar Gehirnzellen-Entzündung, die stets zu bleibenden Schäden, wenn nicht zum Tode führt.

Nach Ablauf von 8 Tagen nach der Injektion bilden sich Rötung und Schwellung zurück, es bleibt dann aber zunächst am Ort der Injektion noch ein kleines gelblich-bräunliches Knötchen zu sehen und zu tasten, das jedoch spätestens nach 21 Tagen vollständig verschwindet.

4

Ein weiterer wesentlicher Vorteil des erfindungsgemäßen Verfahrens ist darin zu sehen, daß durch seine Anwendung eine vaccinale Basisimmunität geschaffen werden kann, die verhindert, an den vorgenannten Komplikationen der bekannten Impfverfahren zu erkranken. Wenn diese Basisimmunität vorhanden ist, dann können alle weiteren Pockenschutzimpfungen nach den üblichen Verfahren nicht mehr zur Gehirnzellenentzündung führen. Das erfindungsgemäße Verfahren ist daher geeignet, die Impfung bei bisher durch Alter oder Krankheit bedingten unumgänglichen Impfhindernissen gefahrlos durchzuführen.

Bayer. Staatsministerium des Innern .5.

2145477

Anlage

zum Schreiben des BAYER. STAATSMINISTERIUMS DES INNERN
vom 15. November 1971 Nr. P 4 - 5173/1 - 671

eingegangen am 26.11.71 Mü 9.12.71

Neue Patentansprüche
zur Anmeldung P 21 45 477.3

1. Impfstoff für die intracutane Pockenschutzimpfung,

d a d u r c h g e k e n n z e i c h n e t ,
daß der Impfstoff aus attenuierten, modifizierten Vaccinia-Viren besteht.

2. Impfstoff nach Patentanspruch 1,

d a d u r c h g e k e n n z e i c h n e t ,
daß der Impfstoff durch Verwendung des Vaccinia-Virus Ankara gebildet ist, das in über 500 Passagen in Hühner-Fibroblasten-Zellen gezüchtet ist.

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EXHIBIT 8

[Logo] **SWISS CONFEDERATION**
Federal Intellectual Property Office

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[Stamp: ETH Library, Zurich]

(19) **SWISS PATENT** A5 (11) **568 392**

(21) Application number: 12972/72

(61) Supplement to: —

(62) Partial application from: —

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(33, 32, 31) Priority: Federal Republic of Germany,
11 September 1971 (2145477)

Patent issued: 15 September 1975

(45) Patent published: 32 October 1975

(54) Title: **Procedure for culturing a virus intended for producing an inoculant against smallpox**

(73) Owner: Free State of Bavaria, represented by the Bavarian Ministry of the Interior (Federal Republic of Germany)

(74) Attorney: George Römpler, Heiden

(72) Inventor: Prof. Dr. med. Anton Helmut Stickl,
Krailing (Federal Republic of Germany)

568392

The invention concerns a process for cultivating a virus intended for producing an inoculant against smallpox.

In the smallpox inoculation which has been common in the past, a highly reactogenic inoculum strain is used, with the virus inserted by epicutaneous scarification. After a certain time interval, an inoculation pustule develops. It is the expression of an infection-allergic process, in which cellular-allergic reactions are primary.

It has been known for a long time that the reactogenicity of an inoculation is not identical to its immunogenicity. That means that severe inoculation reactions need not result in strong protection against infection from the pathogenic variola virus. In recent years, this knowledge has been the reason for introduction of the less reactogenic Elstree inoculation strain, although epicutaneous scarification is still used.

The disadvantage of this type of protective inoculation against smallpox is that in some cases, which are not rare, it results in EEG changes, especially if there has been additional sensitization. The reasons for that are the phylogenetically established functional bridges between the central nervous system and the skin.

For those reasons, the requirements of producing a cutaneous pustule reaction in the smallpox inoculation, and simultaneously to perform a risk-free inoculation appear incompatible, because whenever such an immunoallergic reaction is produced in the skin, it is impossible to prevent the occurrence of associated neuroallergic reactions in the nervous system

Therefore people have attempted to work with so-called "attenuated inoculants". All these attempts assume that normal vaccinia, cultured through 20 to 50 passages on chorioallantoic membrane, and then in relatively high concentration, can be used for inoculation. In fact, passage of the inoculant virus through chick embryos results in

selection of non-uniform inoculum strains, so that an inoculant strain that is essentially more genetically uniform can be obtained after multiple cultures. Furthermore, those inoculants showed a reduction in reactogenicity. That is, the local inoculation reaction was milder and there was less inoculation fever. The proportion of viremia is also distinctly reduced on inoculation with such inoculants. But these methods did not avoid the pustular inoculation reaction. Correspondingly, inoculations with those inoculant strains also exhibited central nervous complications with almost the same expected frequency as after inoculation with conventional inoculants.

Finally, there have also been attempts to inoculate with normal inoculants either subcutaneously (which gave up to 60% swellings in the subcutaneous tissue) or intracutaneously (which also gave pustules as well as tissue necroses).

The intent of the invention is to provide a process for culturing a virus intended as an inoculant against smallpox, which does not have the disadvantages of the previously used virus in known smallpox inoculants.

The process according to the invention is characterized by the fact that the Ankara vaccinia virus is cultured in at least 300 cell culture passages in animal cells until the attenuated vaccinia virus grows on the chorioallantoic membrane in small, strictly proliferative clumps (nodules).

Exemplary embodiments of the process according to the invention are described in the following.

The Ankara vaccinia virus is cultured in at least 300 cell culture passages in animal cells, preferably in more than 500 cell culture passages in chick fibroblast cells or in at least 400 to more than 500 cell culture passages in swine kidney cells. The cell culture passages are continued until the attenuated vaccinia virus grows on the chorioallantoic membrane in small, strictly proliferative clumps or nodules.

The Ankara inoculant is recognized by WHO. It is described in detail in the Handbuch der Schutzimpfungen [Handbook of Protective Inoculations], Springer-Verlag, Berlin, 1965. The Ankara vaccinia virus has also been mentioned in "Strains of Human Viruses" by M. Majer and S. A. Plotkin, S. Karger-Verlag, Basel, 1972 and in the Deutschen Medizinischen Wochenschrift [German Medical Weekly] of 22 November 1974.

An Ankara vaccinia virus cultured in this way is genetically uniform, and its reactogenicity and virulence are attenuated by the cell passages.

One cubic centimeter of the final inoculant, in purified lyophilized form, should contain about 10^7 virus particles. 0.1 to not more than 0.2 cubic centimeters of it is injected intracutaneously. More accurate dosage is possible in this way than with the previously known inoculation procedure. It is also possible to check the process of the inoculation, because the site of the injection shows reddening, slight swelling with a diameter of 4 x 8 mm, and often itching. In no case, though, is there any pustular inoculation reaction. Neither is there any humoral (serum-linked) or tissue sensitization (allergy) in a clinically significant form. However, cellular immunity, which inhibits spread and multiplication in the tissue, is detectable.

When such an inoculant is used, the inoculation reaction progresses without fever and other general injurious phenomena, in contrast to the previously known inoculation procedure with occasional symptoms of illness, such as inoculation fever, inoculation ulcer (abscess), inoculation exanthema (eruption) and even brain cell inflammation, which always causes lasting damages, if not death.

After a period of 8 days following the injection, the reddening and swelling decrease. There is initially a small yellowish-brown nodule that can be seen and felt at the site of the injection, but that disappears completely after no more than 21 days.

Another significant advantage of the procedure according to the invention is that its use can provide a basal vaccinal immunity that prevents sickness from the previously cited complications of the known inoculation procedure. If this basal immunity is present, then all further smallpox inoculations done by the usual procedure no longer cause brain cell inflammation. The procedure according to the invention is therefore suited for inoculating safely persons who have previously had unavoidable barriers to inoculation because of age or disease.

PATENT CLAIM

Process for culturing a virus intended for producing an inoculant against smallpox, characterized in that the Ankara vaccinia virus is cultured in at least 300 cell passages in animal cells, until the attenuated vaccinia virus grows on the chorioallantoic membrane in small, strictly proliferative clumps (nodules)

SUBLCLAIMS

1. Process according to the patent claim, characterized in that the Ankara vaccinia virus is cultured in more than 500 cell culture passages in chick fibroblast cells.

2. Process according to the patent claim, characterized in that the Ankara vaccinia virus is cultured in at least 400, preferably more than 500, cell culture passages in swine kidney cells.

EXHIBIT 9

CONFIDENTIAL EXHIBIT

EXHIBIT 10

CONFIDENTIAL EXHIBIT

EXHIBIT 11

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC A/S, and ANTON MAYR,	)	
Plaintiffs,	)	Civil Action No.
V.	)	05-614 (SLR)
ACAMBIS INC. and ACAMBIS, PLC,	)	
Defendants.	)	

Deposition of PROF. DR. DRES. H.C. JOSEPH STRAUS

Washington, DC

Thursday, November 30, 2006

JOB NO. 177837

PAGES 1-125

Reported by: Denise Vickery, RMR-CRR

November 30, 2006

10:07 a.m.

Deposition of PROF. DR. DRES. H.C. JOSEPH STRAUS, held at the offices of:

BINGHAM McCUTCHEN LLP
The Washington Harbour
3000 K Street NW, Suite 300
Washington, DC 20007-5116

Pursuant to notice, before Denise Dobner Vickery, a Registered Merit Reporter, Notary Public of the District of Columbia.

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I N D E X

Exhibits attached.

court?

A. That's exactly correct, yes.

Q. And at the time that you were working for the Nath firm in Munich, am I correct that you were not admitted to practice law before a German court?

A. That's correct, and I was an Italian citizen all the time.

Q. Have you ever been admitted to practice law in Italy?

A. No.

Q. What was the next position that you held as far as employment after the Nath firm?

A. Well, I made the so-called scientific area at the Max Planck Institute starting with being a so-called scientific collaborator. Then I became head of department.

Q. Hold that thought and we'll come to Max Planck in a minute.

A. Yes.

Q. I thought that you also worked with the Rozenberg firm?

A. This was a collaboration. Rozenberg,

Kestenberg and Nath.

Q. Okay. So from -- am I correct that from 1968 to 1977, you were engaged in this restitution work?

A. Yes.

Q. For a collaborative group of law firms; the Nath, the Rozenberg firm in Tel Aviv, and the Kestenberg firm in New York?

A. Yes.

Q. Did the nature of your work during those years from 1968 to 1977 change?

MR. PENNINGTON: Objection, vague.

THE WITNESS: What does it mean changed?

BY MR. DUNN:

Q. Well, would the nature of your duties -- did the nature of your duties change significantly during that time period, or were you doing the same thing pretty much for that entire time period?

A. Well, it's changed in the sense that I have had both more and more experience, more responsibilities to negotiate with Senator Javits. I corresponded with Vice President Spiro Agnew in the case of the Jews prosecuted from Greece, which were not

really entirely well treated in the entire. So we made the settlement. So that is -- that is the change of responsibilities. Maybe not the legal terms, but it's what the work was at hand.

Q. But the nature of the work continued to be relating to restitution claims?

A. Yes, that's correct.

Q. And the nature -- your status did not change during that time period as far as, for example, becoming admitted to practice law in Germany?

A. No, it didn't.

Q. So throughout that time period from 1968 to 1977, you were not admitted to practice law?

A. That's correct.

Q. Okay. The next position that you held I believe you said was when you went to the Max Planck Institute?

A. I should clarify that I made my Ph.D. at the University of Munich and I was at the Max Planck Institute.

Q. Okay.

A. So I returned practically as a full position

back to the Max Planck Institute.

Q. And what was your entry -- strike that.

When you came back to the Max Planck Institute in 1977, what was your initial --

A. '74 as I said before, yes.

Q. I'm sorry. In 1974 when you came back to Max Planck Institute, what was your initial position at that time?

A. Scientific collaborator. Wissenschaftlicher Mitarbeiter. That's the only position you can have before you become actually head of department or director.

Q. Okay. Scientific collaborator. What did you do?

A. It depends.

MR. PENNINGTON: Objection, vague.

MR. DUNN: Hmm?

MR. PENNINGTON: Objection, vague.

BY MR. DUNN:

Q. Describe your duties.

A. You can be a scientific collaborator dealing with American law.

Q. Excuse me, sir. I want to know what you did.

A. My -- my own, I was involved in unfair competition, patent law and whatever was at hand with the former, I'd say, Eastern European law.

Q. Okay. Since 1977, have you taught any courses that were specific to German civil law?

A. No.

Q. Have you taught any courses that were specific to German personal property?

A. No.

Q. If you refer to Exhibit Number 1 and your qualifications, you note that you: "Beginning in 1989, I have been a visiting professor of law at Cornell Law School, Ithaca, New York."

A. Yes.

Q. Do you see that?

A. Yes.

Q. Sir, I went and checked the Cornell Law School Web site and your name doesn't appear. Can you explain that?

A. I can show you a number of directories of the Cornell Law School where you can find my name.

A. No.

Q. Do you make any reference to it as being additional material that you have reviewed or relied upon?

A. No.

Q. In any of your reports, have you discussed --

A. The only -- the only additional document to which I refer is the report of Professor Tilmann.

Q. Okay. Well, tell me about your meeting with Professor Mayr.

A. Well, I just wanted to see him and to hear how he has been handling, let's say, sending samples to other colleagues and also maybe to the industry.

Q. And why did you want this information?

A. It's always good -- I've learned from Mr. Rozenberg, it's always good to see people to know how to, let's say, estimate them.

Q. Well, what additional information did you expect or hope to be able to obtain from Professor Mayr that you had not already been able to ascertain from your review of the materials?

MR. PENNINGTON: Objection, foundation

and vague.

THE WITNESS: I had, let's say, not -- I was not able to get from neither his deposition, which I of course under the time pressure read it, but there were no -- there was no information of how he handled maybe his relationship with industry.

BY MR. DUNN:

Q. Okay. What questions did you ask him?

A. Well, whether or not he sent materials to companies and if under which conditions, and I should add that, of course, I was not there as deposing Professor Mayr, but as a friendly colleague of him to find out what his attitude is. So it was not a question, have you, did you. So I wasn't and didn't ask. His answer was he actually sent samples also to companies, and it has always been understood that he didn't make any limitations in writing or whatever, but it was understood that after testing, they would negotiate whether or not it would be transfer ownership or whatever licensing agreement. That was new to me and I -- at least to me. Maybe not to others but to me.

Q. He told you -- if I understood your testimony correctly, he told you that it had been his common practice to send out biological samples without there being any written expression of any restriction?

A. I would be careful to use the word common practice, but he named companies like Bayer, if I'm correct. That was one of the leading -- still they are, but not owned any more by Hearst. That he had that kind of a relationship to send them, and then only afterwards to negotiate a question of whether or not something will follow, and that it was understood that without that second, whatever it is, no rights were transferred to those companies.

Q. Let's try to separate out what he may have subjectively understood versus what was objectively stated or put in writing. What I'd like to know is: Did he confirm for you that he had frequently sent out biological samples without there being any written statement placing in writing a restriction on the use of the materials?

MR. PENNINGTON: Objection, vague.

THE WITNESS: I would carefully phrase

that I understood his statement that in the cases where there was some relationship with certain company, that that was the case. That he didn't ask -- didn't impose any written limitations, and it was commonly understood that he was still in control of -- of the ownership.

BY MR. DUNN:

Q. Commonly understood by Dr. Mayr is what he told you?

A. Well, if --

MR. PENNINGTON: Objection, mischaracterizes the testimony.

THE WITNESS: As I understood him.

BY MR. DUNN:

Q. Did you do any investigation to see whether that understanding had also been the understanding of the recipient?

A. I had no opportunity to do that.

Q. Okay.

A. I had no reason to do that.

Q. What else did you discuss with Dr. Mayr or Professor Mayr?

BY MR. DUNN:

Q. Do you have an opinion as to whether or not work that would be done at the Vaccine Institute would have qualified for the professorial privilege?

MR. PENNINGTON: Objection, vague and foundation.

THE WITNESS: If it would be only at the state institutes, it wouldn't be under privilege.

BY MR. DUNN:

Q. And that's because it wouldn't be an institution of higher learning or for another reason?

A. The privilege of Section 42 of the -- the former Section 42 of the Employees Inventions Law was applicable only to the professors, assistants and so-called consultant at the universities.

Q. Okay.

A. And at a certain point in time for the so-called higher facchochschule, which is something in between university and normal higher education. Not applicable to employees of state or not to Max Planck, for instance.

Q. And okay. And would not have been applicable

to the employees of the Vaccine Institute?

A. No.

Q. Okay. Have you seen any documentary evidence indicating that any passaging work was actually performed at the university? As opposed to Vaccine Institute?

A. I believe I've seen some protocols, handwritten protocols, about plaque purification which were of the origin from university. I believe that. I haven't seen anything about the Vaccine Institute.

Q. Have you seen anything that specifically identifies the university? You say you've seen some protocols?

A. I think the protocols were signed by Professor Mayr, and he could sign something only in his capacity as professor and director of the University Institute.

Q. But do those notes indicate where the passaging was physically performed?

A. No.

Q. Okay. So, am I correct that you haven't seen any documentary evidence that shows where physically the passaging of the MVA virus was performed?

A. Not to my recollection.

Q. You state at paragraph 20 page 9 of your first report, Exhibit 1 that "the Vaccine Institute never raised any tangible property claims." You see that?

A. I can -- I can remember that I stated that.

Q. Okay. To your knowledge, who owned the Vaccine Institute?

A. I would say that's a guess, but of course the Bavarian state.

Q. Did the state of Bavaria ever file any patent claims in connection with the vaccine that had been developed?

A. Not to my knowledge. Could be, but I am not aware of any.

(Thereupon, a document was marked for identification Exhibit No. 6.)

BY MR. DUNN:

Q. Handing you what's been marked as Straus Exhibit Number 6, which I'll represent to you is a translation of a Swiss patent issued September 15, 1975. Have you ever seen this before?

A. No.

Q. Directing your attention to the claims at the back, you'll see that it relates to a process for passaging vaccinia virus a number of times. And you'll see that the named inventor is Professor Stickl?

A. Yes, I see that.

Q. You see that the owner of this is the Free State of Bavaria. You see that?

A. Yes.

Q. Would this, sir, be --

A. Sorry. Just a second. Yes.

Q. Would this, sir, be consistent with the work on the smallpox MVA vaccine having been done at the Vaccine Institute?

MR. PENNINGTON: Objection, vague. Objection, foundation. Objection, hearsay, and objection that any testimony about this document would appear to be factual testimony regarding a document that has not been produced before and would not be admissible for that reason.

BY MR. DUNN:

Q. That's for the record. You can answer.

A. It's not a problem to answer that. It

doesn't say anything about that. I mean, he, Stickl knew of the work of Mayr and I could give you a number of examples where people claiming -- I don't know whether my counsel would allow me to tell you that I was involved in a case where Halliburton was demonstrated a prototype by an individual from Pudo Corrado who did not yet file a patent application for that, and they filed before him and the patent attorney for them was named a coinventor.

So I'd just like to say, this doesn't say anything about where the work was done and whether or not Stickl had have learned from -- from Mayr. That's beyond my knowledge, but the fact that you have seen this doesn't say any -- actually nothing about that.

Q. Does this indicate to you, sir, that the state of Bavaria thought that they had some ownership interest in the MVA vaccine that was developed?

MR. PENNINGTON: Same objection as prior stated.

THE WITNESS: Prima facie one could assume.

BY MR. DUNN:

Q. Have you made any investigation as to whether or not the state of Bavaria does have ownership interest in MVA?

A. No.

Q. Now, in your report, Exhibit 1, at paragraph 21 and 22, you essentially dismiss as being irrelevant the vaccine developed because you say that that was 571 and that the relevant virus is MVA 572. Is that a fair paraphrasing?

A. I have to read it. To my understanding, the only thing I stated here is that Professor Stickl, or Dr. Stickl, was in charge of testing and to my understanding had no rights in that physical tangible object talked about.

Q. Well, you say in paragraph 21 that it was MVA 571 that was registered in 1976 in Germany and that was used as the smallpox vaccine?

A. Oh, I see. Yes.

Q. You see that?

A. Yes.

Q. And then you say basically, well, 571 is irrelevant because it's 572 that's at issue?

Q. So, just so we're clear on the record, you're not aware of any evidence of any contemporaneous oral communication between Professor Mayr and Dr. Moss in which Professor Mayr made an express limitation on the use of the strain that was being sent to Dr. Moss?

A. As I stated twice, no.

Q. Let's see if we can talk generally about the extraction principle that you and Professor Tilmann have each discussed in your reports. Okay?

A. Indirectly discussed.

Q. Can you give me an example of a situation where let's assume there has been a valid transfer of ownership. Possession and an agreement to the transfer of ownership. That has occurred.

Under that circumstance, can you give me an example of what would constitute a separate agreement that would be governed by this abstraction principle of German law?

A. Can you repeat the question?

Q. Sure. As I understand it, under German law, there is what's known as an abstraction principle?

A. Yes.

Q. In which you would separately analyze whether there has been a transfer of ownership from whether or not there is some other agreement that may specify terms and conditions, and that under the first analysis, you look at whether there is transfer of ownership that requires change of possession and an agreement to transfer ownership. And if that has occurred, then any other agreement is analyzed separately under this abstraction principle. Is that an accurate statement?

A. That's an accurate statement, yes.

Q. And so let's take that as a hypothetical that ownership has transferred, and let's assume that there is some other agreement between the transferor and transferee. Under that set of principles or that set of assumptions where ownership has transferred, but we have a separate agreement, am I correct that breach of that separate agreement by either party does not change the fact that ownership has transferred?

A. In principle, that's correct. And the question was hypothetical.

Q. Right. I'm just trying to illustrate --

EXHIBIT 12

Lovells

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Our ref.: :
W/jj /O #184031

November 10, 2006

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC A/S,

Plaintiff,

v.

ACAMBIS INC. and
ACAMBIS PLC,

Defendants.

Civil Action No. 05-614 (SLR)

EXPERT REPORT AND/OR LEGAL OPINION OF
PROF. DR. WINFRIED TILMANN

I. INTRODUCTION

1. My name is Winfried Tilmann and I have been retained as a legal expert on German Law by Acambis Inc. and Acambis plc ("Acambis") in connection with the above-referred case in the United States District Court of Delaware ("the Court").

2. I have been asked to study and provide my opinion as to how German Law would view certain issues relating to the ownership of and/or intellectual property rights in certain Modified Vaccinia Virus Ankara ("MVA") strains and vaccines ("MVA-572-strains"). I have also been asked to respond to the Expert Report and/or Legal Opinion that Prof. Dr. Dres. h.c. Joseph Straus has provided in this matter.

3. I understand that Bavarian Nordic (BN) and Prof. Mayr have sued Acambis and have asserted a claim of conversion under U.S. state law. My Expert Report/Legal Opinion does not address U.S. law or whether the U.S. Court will look to German Law concerning any particular issue. My Expert Report/Legal Opinion does provide a critical review of Prof. Straus' Expert Report and/or Legal Opinion, and will try to give the Court a complete understanding of the German Law regarding the question mentioned under ¶ no. 2.

4. In addition to the Expert Report and/or Legal Opinion of Prof. Straus I have read and based my Report/Opinion on the documents listed in Exhibit A, as well as my legal expertise in German Law. I reserve the right to continue to review additional materials that may be made available to me and to supplement this report if I become aware of additional pertinent information or in response to testimony or further reports of others. I have not yet selected or prepared any trial exhibits to supplement my testimony or to illustrate my opinions.

5. I am being compensated in this matter at my usual hourly rate of USD 575 in addition to reimbursement for out-of-pocket expenses. My right to compensation is in no way contingent upon the outcome of the case or any issue in it. I have never testified as an expert and have never been deposed for trial. Further, I have not been retained as or testified as an expert on this subject matter in any other litigation. I have testified as Expert in a hearing of the German Parliament on the Biotech-Patent-Law implementing the Biotech-Patent-Directive of the European Community. Furthermore, I was a longterm member of the Expert-Committee of the German Federal Ministry of Justice for Intellectual Property. Presently I am a member of the Expert Group advising the Ministry of Justice on the future Community Patent. I am regularly being consulted by the said Ministry on matters relating to German, European or international patent law.

II. QUALIFICATION

6. After 4 years of being one of the University assistants of the well-known Prof. Dr. Hefermehl, expert *i.a.* in IP law, I worked for 3 years as a judge at the IP and Antitrust Chamber

of the District Court of Mannheim/Germany, dealing especially with patent and patent-licensing cases. I was then called into the German Ministry of Justice (at that time in Bonn), where I worked in the Patent and Trademark Sections for 10 years (1968-1978). I left the Ministry 1979 to become a partner in the patent-litigation law firm of Dr. von Falck, admitted to the Oberlandesgericht Düsseldorf (Appeal Court). Since that time I have been active as an appeal lawyer with a wide experience in all fields of IP law, especially patent law, including all aspects of transfer, assignment and licensing of IP-rights.

7. I have completed my doctorate and my *Habilitationsschrift* (to become professor) at the University of Heidelberg and became Adjoint Professor and member of the Law Faculty in the 1970's. I have been teaching IP and Antitrust Law (national and European) since 1975 at Heidelberg University. I have published more than 100 books and articles. One of the topics of my specific scientific interest is the relation between IP-Law and general civil law (torts, unlawful enrichment, transfer, licensing). A copy of my curriculum vitae and a list of my publications are attached as Exhibit B.

8. I am a member of the Board of Directors of the European Patent Lawyers Association (EPLAW), a member of the Board and of two Committees of the German Association for Industrial Property and Copyright Law (GRUR) and President of the Legislative Committee on IP and Copyright Law of the German Lawyers Association (DAV).

III. Expected Testimony and Opinion

9. I am prepared to testify that a transfer of ownership rights regarding MVA vaccines stock and MVA viral stock took place between Prof. Mayr and Dr. Moss/NIH. Under German Law the change of ownership, would have been independent (*abstract*) from any separate agreement defining, limiting or restricting the purpose that the MVA was to be used for ("purpose-agreement") (if there was such a purpose-agreement stipulated between Prof. Mayr and Dr. Moss).

10. I am prepared to testify that, because of the independent (*abstract)* nature of an ownership-transfer under German Law and the unconditional nature of the ownership of the transferee (Dr. Moss and his Institute, the NIH) the ownership-transfer to Acambis was also valid.

IV. My opinion regarding the transfer of ownership of biological material from Prof. Mayr to Dr. Moss (and his Institute)

Rechte an einer Sache unterliegen dem Recht, in dem sich die Sache befindet.

This *lex rei sitae*, therefore, would require a German court to apply German Law.

15. In governing the transfer of ownership German Law would apply the rule regarding the so-called "abstract" (independent) nature of the transfer of ownership (*Bundesgerichtshof – BGH – Neue Juristische Wochenschrift – NJW– 1996, page 2233/2234*). Under this rule the transfer of ownership is separate and independent from whether there is also any underlying obligatory purpose-agreement (*causa*). Under German Law, due to its independent nature, a transfer of ownership remains valid independent of whether any obligations arising out of any valid obligatory purpose-agreement are fulfilled or not fulfilled by the obliged party (*Palandt/Helfrich, Bürgerliches Gesetzbuch, 65th edition 2006, EGBGB Art. 43 Nr. 3 with further references to German court decisions).*

16. The so-called *Abstraktionsprinzip* (principle of the abstract nature of ownership-transfer) is also accepted by Prof. Straus as being valid for the present case (¶ no. 30 of his Opinion). The effect of this principle is that one has only to ask, in the present case, whether the specific conditions for the change of ownership are met. If they are met, the change of ownership has taken place, irrespective of any underlying aim, wish, understanding or even agreement as to what purpose the transfer should serve. The reason for the *Abstraktionsprinzip*, a speciality of German Law, is to provide legal security for third parties who want to acquire ownership from the transferee (*Erman/Palm, BGB 11th ed. 2004 Einl. § 104 Nr. 21: the real importance of the principle is in respect to third parties; the law wants to keep the abstract transfer-agreement free from deficiencies of the causal agreement [translation]*); the principle is still regarded as useful (*Rother, Archiv für die civilistische Praxis, vol 169, page 1 seq.; Grigoleit, Archiv für die civilistische Praxis, vol. 199, page 379 seq.; Palandt, op.cit Überblick vor BGB § 104 Nr. 22).*

17. Accordingly, the only question under German Law is whether the conditions for a change in ownership of the vials of MVA transferred to Dr. Moss/NIH have been met. For an ownership-transfer, according to § 929 BGB (*Bürgerliches Gesetzbuch* – Civil Code), there need only be two elements: (1) change of possession and (2) agreement as to the transfer of ownership of the specific personal property transferred.

18. As to the first element (1), Prof. Mayr has undisputably given up any possession (*Besitz*, in the meaning of actual power) over the MVA-572 strains provided to Dr. Moss/NIH. After the request of Dr. Moss the MVA materials were sent at the end of August 2001 to Dr.

Moss/NIH, thus relinquishing every "actual power", direct or indirect, over these strains on the side of Prof. Mayr ("*In response to your request for an early sample of vaccinia Virus MVA I was happy to provide you with the material....This virus material has been stored at the institute under my control since [1974].*" Prof. Mayr's letter to Dr. Moss dated September 12, 2001). This is not disputed by Prof. Straus, who does not even mention this first element (change in possession), and it cannot be disputed: The MVA strains were now in the U.S. Prof. Mayr remained in Germany, not able to exercise actual power over these strains. Prof. Straus, in his Opinion, discusses only the second element (agreement as to the change in ownership, ¶ no. 31, 32, 35 of his Opinion).

19. This leaves the second element (2) of a transfer-agreement (see ¶ no. 17 above): agreement as to the transfer of ownership of the specific personal property transferred. The facts speak for themselves: Prof. Mayr sent the MVA strains to Dr. Moss/NIH at the end of August 2001 without any commentary, especially not suggesting that Dr. Moss should return them or otherwise refrain from exercising ownership over the strains. He clearly did not want these MVA strains returned, because they were to be used by the recipient. Nor did Prof Mayr in his letter of September 12, 2001, sent to Dr. Moss after having sent the material to him, request any return of the changed or unchanged material. He had sent these MVA-strains once and for all.

20. This and the acceptance of the material and the letter of September 12, 2001 by Prof. Mayr can only be understood and interpreted as establishing an agreement regarding transfer of ownership. It was neither a lease (where there is no change in ownership because there is a duty to hand back the material), nor a service contract (no change in ownership, duty to hand back the material). Prof. Mayr gave the material and did not expect to see his "property" preserved, which would include a right on his side to call the material back. That Prof. Mayr gave up possession is given. Prof. Mayr also clearly wanted Dr. Moss/NIH to "have and to use" the MVA-572 strains. This fulfilled the necessary elements for transfer of ownership (the latter being defined in § 903 BGB as being able to do with the object what you want and to exclude others from any intrusion).

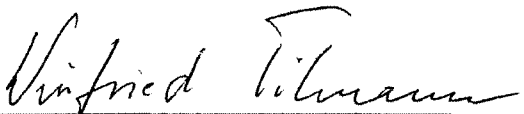
21. If we now look at the arguments of Prof. Straus in ¶ no. 29 seq. of his Opinion, they start out with the correct statement that German Law requires a "separate" (*abstract*) transfer of ownership (¶ no. 29). As explained above, there was a transfer of ownership, and such a transfer is recognized under German Law as being separate from any "sales contract" or other agreement as to the reason for the transfer, such as a "purpose-agreement".

agreement (binding the transfer-agreement together with any purpose-agreement, if the latter were existent; making it – under the said assumption – three agreements: transfer-agreement, purpose-agreement, binding-together-agreement). Not applicable is the legal figure of a conditioned (deferred) transfer of ownership (dependent, e.g., from a payment), since, in the present case, the acquisition of ownership by Dr. Moss/NIH was not dependent on (deferred until) a certain action of Dr. Moss/NIH. An "automatic" fall back of a transferred ownership, dependent on a resolutory condition, is not known in German Law. A "fall back" would necessitate a new (second) transfer-of-ownership-agreement between Dr. Moss/NIH and Prof. Mayr, which is not existent and also not referred to by Prof. Straus.

30. Since none of the three possible exceptions is applicable, the *Abstraktionsprinzip* is applicable in the present case.

31. For these reasons, if called, I will testify that under German Law, (1) Prof. Mayr has transferred ownership of the strain MVA-572 to Dr. Moss/NIH enabling a valid further transfer to Acambis; (2) there has been no explicit purpose-agreement between Prof. Mayr and Dr. Moss; (3) the question, whether such an agreement existed and what content it had, is irrelevant for the validity of the transfer-of-ownership from Prof. Mayr to Dr. Moss/his Institute and the further transfer to Acambis; and (4) if there had been an explicit purpose-agreement between Prof. Mayr and Dr. Moss the only remedy under German Law for breach of such an agreement would be against Dr. Moss/NIH and not against third parties such as Acambis.

Respectfully submitted,



Prof. Dr. Winfried Tilmann

EXHIBIT 13

CONFIDENTIAL EXHIBIT

EXHIBIT 14

EXHIBIT 7

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Bethesda, MD 20892-0445
Phone: 301-496-9869; Fax: 480-1147
Email: bmoss@nih.gov

August 3, 2001

Prof. Anton Mayr
Lehrstuhl für Mikrobiologie und Seuchenlehre
Ludwig-Maximilians-Universitat Munchen
Veterinaerstr. 13
80539 Muenchen
GERMANY

Dear Prof. Mayr,

Gerd Sutter told me the good news that you have been able to locate an early sample of MVA in your freezer and have agreed to send it to me. I wish to thank you for your generosity in this regard. As you are aware, MVA has taken on a new life as the premier vaccinia virus vector. I have enclosed a reprint of a recent paper that clearly illustrates the great potential value of MVA.

I understand that Gerd will help with the shipping of the MVA. He has also indicated that he is willing to help with a draft of a letter of authentication of the MVA in order to satisfy the regulatory agencies here.

Again, I thank you for your kindness in this matter.

Sincerely yours,

Bernard Moss

Bernard Moss M.D., Ph.D.
Chief, Laboratory of Viral Diseases

cc: Dr. Gerd Sutter

EXHIBIT 15

e No.—

8/30/01 - Hood in room 208 (Hood # 375) began decontaminated (receipt attached)
8/31/01 Certified - Hood Steel Nanker #375)
Receipt attached.

Received from Bird Sutter (from Anton Mayr) 8/23/01 (was before 8/30/01)
mail labeled:
MVA 572. FHE v 22.2.74.
1 mL
Titer 10^8 TCID50
(see attached letter)
Stored in Rack II MVA Stocks

9/11/01 Received SPAFAS premium eggs (distributed by B+E Eggs, Ephrata, PA 17522 (see receipt)

9/12/01 Norm made CEF with media as listed. E-MEM, 10% FBS, glutamine, streptomycin + neomycin (5 mL/500 mL bottle) Lot + Numbers, expiration dates listed

9/21/01 - Using 9/12 flask, CEF made cells in 24 well plates. (made regular way - 1 T-150 = 60 mL & also did 1:2 - 1 flask & stuffing 2 cells.

9/22/01 Removed mail from Dr. Mayr - labeled above. Added 1 mL sterile H_2O.
Did 10 fold dilns - from each 10 fold dilns did .5 log dilns (.1 mL in .21 mL, .3 in .63 mL. Plated out dilutions on sheet. (.1 mL/24 well.

9/25/01. Read wells for CPE as of 9/24 shut
9/26/01 - 4th day 4 harvested by scraping well

To Page No.—

Read, Witnessed & Understood by me.	Date	Invented by	Date
		Recorded by	

EXHIBIT 16

CONFIDENTIAL EXHIBIT

EXHIBIT 17

CONFIDENTIAL EXHIBIT

EXHIBIT 18

CONFIDENTIAL EXHIBIT

EXHIBIT 19

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EXHIBIT 20

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CONFIDENTIAL EXHIBIT

EXHIBIT 26

CX-262C:1

EXHIBIT 14

Prof.Dr.Dr.h.c.mult.Anton Mayr
Lehrstuhl für Mikrobiologie und Seuchenlehre
Ludwig-Maximilians-Universität München

80539 München
Veterinärstraße 13
Tel. 089/2180-2532

12. September 2001

Bernard Moss M.D., Ph.D.
Chief, Laboratory of Viral Diseases
NIAID, National Institutes of Health
Building 4, Room 229
Bethesda, MD, 20892-0445
USA

Dear Professor Moss,

In response to your request for an early sample of vaccinia Virus MVA I was happy to provide you with the material MVA 572. FHE - 22.02.1974.

This virus material represents lyophilized tissue culture material from the 572nd passage of MVA on primary chicken embryo fibroblasts harvested February 22, 1974 and originates from the vaccinia virus MVA developed and passaged at the Institut für Mikrobiologie und Infektionskrankheiten der Tiere, Ludwig-Maximilians-Universität München (see Mayr *et al. 1975, Passage history, pro partus and applicability of the attenuated vaccinia virus strain MVA*, Infection 3:6-14).

Propagation in chicken embryo fibroblasts through two plaque purification passages (MVA 569.FHE - 12.02.74 and MVA 570. FHE - 15.02.74) and an amplifying passage (MVA 571. FHE - 19.02.74) resulted in the virus stock MVA 572. FHE - 22.02.1974 which was titrated (original titer $10^{8.25}$ $TCID_{50}$/ml) and lyophilized as standard MVA seeding material. This virus material has been stored at the institute under my control since that time.

With best regards.

Sincerely yours,

Dr. Mayr

Prof.Dr.Dr.h.c.mult.Anton Mayr

EXHIBIT 27

CONFIDENTIAL EXHIBIT

EXHIBIT 28

CONFIDENTIAL EXHIBIT

EXHIBIT 29

CONFIDENTIAL EXHIBIT

EXHIBIT 30

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC a/s and ANTON MAYR,

Plaintiffs,

vs. : Civil Action No. 05-614

ACAMBIS INC. and ACAMBIS PLC,

Defendants.

Washington, D.C.
Thursday, November 30, 2006

Deposition of:

LOUIS P. BERNEMAN,

called for oral examination by counsel for Plaintiff, pursuant to notice, at Venable LLP, 575 7th Street, N.W., Washington, D.C., before Ronald E. Bennett, of Capital Reporting Company, a Notary Public in and for the District of Columbia, beginning at 9:30 a.m., when were present on behalf of the respective parties:

APPEARANCES

On Behalf of Plaintiff
DAVID M. LUBITZ, ESQUIRE
Bingham McCutchen
3000 K Street, N.W., Suite 300
Washington, D.C. 20007-5116
202-373-6716

On Behalf of Defendants
WILLIAM D. COSTON, ESQUIRE
Venable LLP
575 7th Street, N.W.
Washington, D.c. 20004-1601
202-344-4813

CONTENTS

Page 65, Line 4 through Page 69, Line 12, have been designated For Attorneys' Eyes Only.

PROCEEDINGS

Whereupon,
LOUIS P. BERNEMAN,
called as a witness, and having been first duly sworn, was examined and testified as follows:
EXAMINATION BY COUNSEL FOR PLAINTIFF
BY MR. LUBITZ:
Q. Good-morning, Mr. Berneman. For the record, David Lubitz, counsel for Bavarian Nordic. Mr. Coston?
MR. COSTON: Bill Coston for Acambis, with the Venable firm.
Q. Mr. Berneman, you have been submitted as an expert witness on behalf of Acambis in the case currently under consideration. Is that correct?
A. Yes.
Q. And I will mark -- ask that a copy of the report be marked as Exhibit 1 to show to counsel.
(Berneman Exhibit Number 1 was marked for identification.)
BY MR. LUBITZ:
Q. I just ask you to take a look at it and

tell me whether that is an accurate copy of the report that you submitted in connection with this case.
(Pause.)
A. Yes, sir, it is.
Q. Did you review this report and its appendices in preparation for this deposition today?
A. Yes.
Q. When did you do that?
A. During the past week or so.
Q. Did you review any other documents outside of the expert report and appendices in preparation for your testimony today?
A. Yes.
Q. And what documents are those?
A. Documents listed in Appendix B of my report.
Q. Other than the documents listed in Appendix B, did you review any other documents in connection with your testimony today?
A. Yes.
Q. And what documents are those?

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that is a fair statement.
A. The answer to that question is yes.
Q. And what is the custom and practice?
A. The custom and practice is twofold. One, that is the recipient acknowledge the provider of the material in any publications. And two, material is exchanged or is transferred without limitation as to use or restriction as to distribution unless if there is an agreement to thereby limit or restrict.
Q. Do I understand you to mean, that if a scientist at one institution transfers materials at the request of a scientist at another academic institution, that it is customary for there to be an agreement. And that absent such an agreement there are no restrictions on transfer of materials?
MR. COSTON: Object to the form of the question. Misstates prior testimony.
A. I'm not suggesting that it is necessarily custom and practice for there to be an agreement. My answer was, that the custom and practice is twofold. One, that the recipient acknowledge the provider in publications.

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And two, that the recipient is -- the recipient is not limited as to how that individual uses the material or what that individual does with the material with respect to transfer distribution restriction unless there is an agreement with respect to any such limitations or restrictions.
Q. In your experience, do the agreements that you refer to -- must the agreements that you refer to occur before the material is transferred?
A. Yes.
Q. In your experience -- let me ask you specifically -- you worked for 10 years at the University of Pennsylvania. Is that right?
A. Yes.
Q. And you were managing director of the Center for technology transfer at the university?
A. Yes.
Q. In that capacity you have administered -- you were the intellectual property administrator for the University of Pennsylvania. Is that correct?
A. Yes.
Q. Did you ever come across a situation while

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at the University of Pennsylvania where a scientist affiliated with the University of Pennsylvania had transferred material to another nonprofit research institution without -- prior to executing material transfer agreement.
(The reporter read back as requested.)
THE WITNESS: I believe the premise of your question was, did I ever come across. I believed then, I believe now, I understood then and I understand now, that many biological materials were transferred both from and to researchers at the University of Pennsylvania from and to researchers at academic research, non-profit research institutions teaching hospitals on a global basis outside of any written agreement.
Q. You were going to say?
A. I was not a party to that transfer. The university was not a party to that transfer. So I didn't come across. But it was a general understanding and is a general understanding in my field that such transfers are routine and common place.

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Q. While at the University of Pennsylvania you were aware of situations in which researchers at the University of Pennsylvania transferred to researchers at other academic or nonprofit institutions biological materials without benefit of a material transfer agreement; is that correct?
A. Yes.
Q. Approximately how often did this occur in the 10 years that you were at the University of Pennsylvania?
A. I have no way of giving you an exact answer to that question.
Q. I'm not asking for an exact answer. You agree that you were aware of such situations. I would just like a ballpark as to whether this occurred on a daily basis, a weekly basis, a monthly basis, an annual basis?
A. During my 10 year tenure at Penn, the office that I managed entered into approximately 5,000 material transfer agreements. We estimate that a number greater than that occurred outside of the material transfer agreement.

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Q. You have no way of estimating for me how many transfers occurred outside of a material transfer agreement?
A. My belief is that more transfers occurred at least early than more transfers occurred in the early years I was there informally than occurred formally under a material transfer agreement.
Q. With respect to the informal transfers, did you, as administrator, as intellectual property administrator at the University of Pennsylvania, ever seek to assert rights on behalf of the University of Pennsylvania after one of these informal transfers took place?
A. No.
Q. And so it's your testimony that whenever materials were transferred informally, whatever rights the University of Pennsylvania might have had in those materials evaporated with the transfer. Is that correct?
MR. COSTON: Object to the form of the question.
A. Rights with respect to the tangible

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property itself evaporated. Rights with respect to intellectual property rights may not have evaporated subject to the one-year grace period in the United States.
Q. What do you mean by the one-year grace period in the United States?
A. It is my understanding that in the United States there is a one-year grace period for absolute novelty with respect to filing patent applications.
Q. So when you say intellectual property rights, are you limiting yourself to patent rights?
A. Yes.
Q. Excepting patents rights, is it your contention that, while at University of Pennsylvania as intellectual property administrator that any informal transfer of materials caused University of Pennsylvania to forfeit any rights? Again, excepting patents rights in those materials?
MR. COSTON: Object to the form of the question.
A. I don't know what you mean by any rights. Certainly the rights to -- the right to use and to

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further distribute the material were forfeited absent an agreement otherwise.
Q. Do those forfeited rights include the rights to commercialize the material?
A. To the extent that the university could commercialize, the university still enjoyed those rights. But with respect to the rights of others to use the material in whatever means they sought to use the material, they wished to use the material, was not restricted.
Q. Let me ask you about the 5,000 material transfer agreements that you were responsible for at the University of Pennsylvania. To your knowledge, did any of those 5,000 material transfer agreements -- were any of those material transfer agreements executed after an employee of the University of Pennsylvania transferred the material that was the subject of the material transfer agreement?
A. That 5,000 figure is an approximate number. The instructions on material transfer agreements themselves instruction to my staff,

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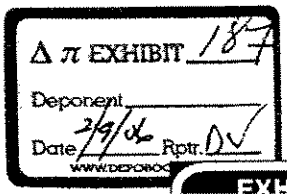
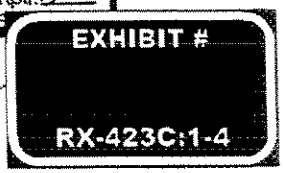
instructions to researchers, specify, make explicit that materials may only be transferred following receipt of an executed material transfer agreement.
Q. So are you saying that to your knowledge you cannot think of a single material transfer agreement while at the University of Pennsylvania that was executed after the material that was the subject of the agreement was transferred by an employee of the University of Pennsylvania?
A. That's correct, to my knowledge.
Q. Are you aware of any case while you were at the University of Pennsylvania in which an employee or affiliate of the University of Pennsylvania transferred materials to another academic or research institution that was followed up by an agreement setting forth tangible or intellectual property rights in the material?
MR. COSTON: Object to the form of the question.
A. Yes.
Q. And could you please describe the instances that you are aware of.

EXHIBIT 31

CONFIDENTIAL EXHIBIT

EXHIBIT 32





From: Michael Mowatt [MMOWATT@niaid.nih.gov]
Sent: Tuesday, May 28, 2002 4:04 PM
To: 'Peter Wulff'
Subject: RE: 8 Apr 2002 facsimile to Dr. B. Moss

Peter,

I write to confirm my receipt last week of your letter, dated 13 May 2002, and the enclosures, which include 1) your 9 Apr 2002 facsimile transmittal to Dr. L. Gritz (Therion), on which Drs. B. Moss and A. Mayr received courtesy copies, 2) Dr. Gritz's 10 Jan 2002 letter to Dr. Mayr, and 3) Dr. Gritz's 26 Feb 2002 letter to Dr. Mayr. Thank you very much for supplying these documents.

As I mentioned in my electronic mail message of 10 May (below) I have found no evidence of the "stringent" material transfer agreement you mentioned during our conversation on 19 April. Instead, our records pertinent to the transfer of the MVA stock from Dr. Mayr to NIAID include only Dr. Mayr's 12 September 2001 letter to Dr. Moss. Likewise, I have found no evidence of an agreement between NIAID and Bavarian Nordic that relates to or would limit in any way NIAID's use or distribution of the MVA stock supplied by Dr. Mayr. Accordingly, since you have supplied no documentation to the contrary and in light of the pressing worldwide public health need I mentioned previously, NIAID will continue its vaccine research and development activities as planned.

Again, on behalf of the National Institute of Allergy and Infectious Diseases I would like to express my sincere appreciation of your assistance with this matter. Please let me know if you have any questions or if I can assist you further.

Regards,

Michael

> -----Original Message-----
> **From:** Peter Wulff [mailto:pw@Bavarian-Nordic.dk]
> **Sent:** Friday, May 10, 2002 9:21 AM
> **To:** 'Michael Mowatt'; Peter Wulff
> **Subject:** RE: 8 Apr 2002 facsimile to Dr. B. Moss
>
> Dear Michael Mowatt,
>
> I am very sorry that I have not attended to this matter. I have been travelling a lot the last few weeks. I shall send the letter copies from Therion Monday. My secretary has left for today.
>
> Best regards
>
> Peter Wulff
>
> > -----Original Message-----
> > **From:** Michael Mowatt [mailto:MMOWATT@niaid.nih.gov]
> > **Sent:** 8. maj 2002 22:05
> > **To:** 'Peter Wulff'
> > **Subject:** RE: 8 Apr 2002 facsimile to Dr. B. Moss

Importance: High

Peter,

I write to confirm that I have not yet received from you the documents we discussed on 19 April and which I listed in my 24 April message (below) to you. However, since we last spoke on 19 April I have had an opportunity to gather information and documentation relevant to our discussion.

During our conversation you mentioned that Dr. Mayr provided the material to Dr. Moss under a "stringent" material transfer agreement. I have been unable to locate such an agreement. Instead, according to our records Dr. Mayr provided the material, "MVA 572.FHE - 22.02.1974," under cover of a letter, dated 12 September 2001, that describes the passage history of the lyophilized virus stock that he supplied to Dr. Moss. The letter specifies no limitations on NIAID's use of the materials. We understand that Dr. Mayr had full authority to transfer the material to NIAID. Your suggestion during our 19 April conversation that Bavarian Nordic negotiated an exclusive consulting arrangement with Dr. Mayr, and not with his employer, supports our understanding. I would be pleased to provide to you a copy of Dr. Mayr's 12 September letter.

In addition, according to our records the NIAID has not entered into any agreement with Bavarian Nordic that relates to NIAID's use or distribution of the materials that were the subject of your 8 Apr 2002 facsimile transmittal to Ms. Linda Gritz.

As you are aware research on and development of vaccines, particularly vaccines to combat smallpox and HIV infection, are top priorities for NIAID. In light of the urgent worldwide public health need for such vaccines, and based on the documentation noted above, NIAID will continue its research and development efforts as planned.

Thank you very much for your assistance with this matter. Please do not hesitate to contact me if you have any questions or concerns.

Regards,

Michael

-----Original Message-----
From: Michael Mowatt
Sent: Wednesday, April 24, 2002 4:59 PM
To: 'Peter Wulff'
Subject: RE: 8 Apr 2002 facsimile to Dr. B. Moss

Peter,

It was a pleasure to speak with you last Friday on the subject of MVA. I truly appreciate your efforts to assist me in gathering information about the materials that A Mayr provided to B Moss.

I understood from our conversation that you would provide to me this week by facsimile transmittal several pertinent documents. I write to confirm that you will provide the following:

1) 10 Jan 2002 letter from L Gritz to A Mayr
2) 26 Feb 2002 letter from L Gritz to A Mayr

3) Agreement(s) under which A Mayr has transmitted materials to B Moss

In addition to these documents I was hoping you could provide more information about the nature of A Mayr's relationship with Bavarian Nordic. I think this will help clarify the context in which the transfer of materials took place.

Thank you again for your helpful assistance. I look forward to hearing from you this week.

Regards,

Michael

-----Original Message-----
From: Peter Wulff [mailto:pw@Bavarian-Nordic.dk]
Sent: Friday, April 19, 2002 5:12 AM
To: Michael Mowatt; Peter Wulff
Subject: RE: 8 Apr 2002 facsimile to Dr. B. Moss

Dear Mr. Wulff,

I can now see why you have questions, since you never received copies of the letters sent by Therion (Linda Gritz) to Anton Mayr. Let us talk about it over the phone. You may call me today between 8 and 11 am your time on +45 33 26 83 83.

Regards

Peter Wulff

-----Original Message-----
From: Michael Mowatt [mailto:MMOWATT@niaid.nih.gov]
Sent: 16. april 2002 15:50
To: Peter Wulff (E-mail)
Subject: 8 Apr 2002 facsimile to Dr. B. Moss
Importance: High

Peter Wulff,
CEO, Bavarian Nordic A/S

Dear Mr. Wulff,

I attempted to reach you by telephone today but learned that you will be out of the office until Thu, 18 Apr 2002.

Dr. Bernard Moss, an investigator in the Division of Intramural Research at the National Institute of Allergy and Infectious Diseases (NIAID), has forwarded to me your 8 Apr 2002 fax to Ms. Linda Gritz, which you provided to him as a courtesy copy

("cc"). I have several questions about this correspondence and would like to discuss it with you at your earliest convenience.

I would be pleased to call you on Thu, 18 Apr or Fri, 19 Apr at a time that is convenient for you. By my calculations you are six hours ahead of us here (http://www.worldtimeserver.com/). Please let me know your availability to discuss this matter.

Thank you very much for your assistance. I look forward to speaking with you soon.

Regards,

Michael R. Mowatt, Ph.D.
Director, Office of Technology Development

National Institute of Allergy and Infectious Diseases
National Institutes of Health
U.S. Department of Health and Human Services

Building 31 Room 3B62 Tel: 301/496-2644
31 Center Drive MSC 2137 Fax: 301/402-7123

Bethesda MD 20892-2137
http://www.niaid.nih.gov/ttb/ttb.htm

EXHIBIT 33

CONFIDENTIAL EXHIBIT

EXHIBIT 34

CONFIDENTIAL EXHIBIT

EXHIBIT 35

EXHIBIT 13

Received by BN A/S 04 JUN 2003

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Laboratory of Viral Diseases, NIAID
National Institutes of Health
Building: 4, Room: 229
4 Center Drive, MSC 0445
Bethesda, MD 20892-0445
Phone: 301-496-9869; Fax: 480-1147
Email: bmoss@nih.gov

23 April 2003

Prof. Dr. Dr. h.c. mult. Anton Mayr
Lehrstuhl fur Mikrobiologie und Seuchenlehre
Veterinarstrasse 13
80539 Munchen
GERMANY

Dear Professor Mayr,

At the request of Dr. Michael Mowatt, Director of the Office of Technology Development at the National Institute of Allergy and Infectious Diseases (NIAID), I have not previously responded to your letter to me, dated 6 November 2002, regarding "MVA and uses thereof." Dr. Mowatt's request stemmed from the very positive meeting held on 8 January 2003 meeting in Bethesda, Maryland with Drs. Peter Wulff and Paul Chaplain of Bavarian Nordic A/S. I understand that the 8 January meeting, which included Drs. John La Montagne, Carole Heilman and Pamela McInnes as well as Ms. Cindy Fuchs and Dr. Mowatt of the NIAID, yielded fruitful discussion of the respective positions of the NIAID and Bavarian Nordic in regard to NIAID's use and distribution the MVA 572.FHE – 22.02.1974 that you provided to me in late summer 2001. Specifically, I understand that Drs. Wulff and Chaplain were to relay to you the amicable conclusions reached during the meeting. In this context I was both surprised and disturbed by Dr. Wulff's letter, dated 27 March 2003, to Dr. John La Montagne of the NIAID (enclosed). For this reason I feel it necessary at this time to address the inaccuracies reflected in your 6 November 2002 letter to me.

Dr. Gerd Sutter brought the F6 isolate of MVA to the National Institutes of Health (NIH) after he received an AIDS scholarship from the Bundesministerium für Forschung und Technologie to work in my laboratory. In 1992, Dr. Sutter and I reported that MVA expressed both vaccinia viral and recombinant proteins at a high level in non-permissive human cells and suggested that MVA would make a safe and efficient vector for vaccines [Sutter and Moss, PNAS 89, 10847,1992]. These claims were substantiated in a series of animal protection experiments over the next several years [for example: Sutter et al. Vaccine, 12, 1032, 1994; Wyatt et al. Vaccine 14, 1451, 1996; Carroll and Moss Virology 238, 198, 1997; Durbin et al Vaccine 16, 1324, 1998; Wyatt et al. Vaccine 18, 392, 1999; Stittelaar et al. J. Virol. 74. 4236, 2000; Amara et al. Science 292, 69, 2001; Earl et al. Virology 294, 270, 2002]. Although the F6 strain was perfectly good for "expression vector work" in the laboratory, it did not have a well-documented passage history. I contacted you in 1995 to request MVA from an original vial of either a vaccine lot or a master seed for the purpose of producing recombinant vaccines for clinical use. In response to my request you generously provided MVA 575 and MVA II/85 without any restrictions. Because the U.S. Food and Drug Administration had expressed concern about the theoretical possibility that the causative agent of bovine spongiform encephalopathy (BSE) was a contaminant in MVA preparations made in the 1980's, I

subsequently requested a vial of an earlier lot. In response to my request you generously provided MVA 572 in the summer of 2001, again with no restrictions. I never received MVA from the European tissue culture collection or from Bavarian Nordic, and therefore am not aware of any restrictions or licenses that you may have placed on the distribution of materials provided to these organizations.

In your 6 November 2002 letter to Dr. La Montagne, you expressed concern regarding the safety profile of the MVA that you provided to me. I must assume that your concerns arose after you shipped MVA 572 to me, as you failed to mention any such concerns whatsoever in the letter, dated 12 September 2001, that you provided to me in response to my request for documentation about the MVA 572 you shipped in the summer of 2001. Nevertheless, I assure you that, before testing in clinical trials any derivatives of MVA 572, the NIAID will undertake, at a minimum, all testing necessary to meet safety standards mandated by clinical regulatory authorities.

I am enclosing a package of reprints describing my studies over the years with MVA. You will see that I have referenced your publications numerous times in order that you receive recognition for your seminal work. I believe that we are all striving toward the goal of enhancing the health and security of the peoples of the world.

Sincerely yours,

Bernard Moss

Bernard Moss M.D., Ph.D.
Chief, Laboratory of Viral Diseases
Division of Intramural Research, NIAID

Enclosures

cc: P Wulff, Bavarian Nordic A/S, via facsimile transmittal: +45 33 26 83 80 without enclosures
J La Montagne, Deputy Director, NIAID without enclosures
M Mowatt, Office of Technology Development, NIAID without enclosures
S Sherman, Office of the General Counsel, NIH without enclosures
M Rohrbaugh, Office of Technology Transfer, NIH without enclosures

A. Mayr
23 Apr 2003

TOTAL P.

EXHIBIT 36

CONFIDENTIAL EXHIBIT

EXHIBIT 37

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EXHIBIT 38

CONFIDENTIAL EXHIBIT

EXHIBIT 39

fax

To
Linda Gritz

Fax No.
+1 617 876-9391

From
Peter Wulff
Bavarian Nordic A/S

Date
9 april, 2002

Pages incl. cover
1

Dear Linda Gritz,

I have from Prof. Anton Mayr received copies of your letters to him dated January 10 and February 26, 2002.

As you know Bavarian Nordic bases many of its programs on MVA and has spend years on further developing MVA and has during this cause developed additional derivatives MVA.

Prof. Anton Mayr has been an exclusive consultant to Bavarian Nordic for many years in the field of MVA, and Bavarian Nordic has acquired all remaining stocks of the actual vaccine vials and master seeds developed and produced of MVA which were in the possession of Prof Mayr.

As you will appreciate Bavarian Nordic is very protective about its MVA and therefore we can regrettably not permit Bernie Moss to give you the requested virus.

When this is said we would welcome business discussions with Therion relating to commercialisation of MVA in the USA, both as a safe smallpox vaccine and as recombinant vaccines.

With best regards,

Sincerely,

Peter Wulff
CEO
Bavarian Nordic A/S
Vester.....
pw@bavarian-nordic.dk

cc: Prof. Bernard Moss 001 301 480 1147
Prof. Anton Mayr

EXHIBIT 40

CONFIDENTIAL EXHIBIT

EXHIBIT 41

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

OFFICE OF TECHNOLOGY
DEVELOPMENT

Building 31 Room 3B62
31 Center Drive MSC 2137
Bethesda MD 20892-2137

Tel: (301) 496-2644
Fax: (301) 402-7123

15 July 2002

→ PCH

VIA FACSIMILE TRANSMITTAL WITH CONFIRMATION VIA COURIER

Fax +45 33 26 83 80, Tel +45 33 26 83 83

Peter Wulff
Bavarian Nordic A/S
Vesterbrogade 149
DK-1620 Copenhagen V
DENMARK

RE: MVA 572.FHE – 22.02.1974

Dear Mr. Wulff:

I write to summarize my understanding of the conditions under which the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health received from Prof. Dr. Dr. h.c. mult. Anton Mayr, Lehrstuhl für Mikrobiologie und Seuchenlehre, Ludwig-Maximilians-Universität München, the lyophilized preparation of vaccinia virus MVA known as "MVA 572.FHE – 22.02.1974." In addition, I write to confirm the NIAID's intention to use and make available to other parties progeny and derivatives of the material that have been developed by Dr. Bernard Moss, Chief of the Laboratory of Viral Diseases, Division of Intramural Research, NIAID.

As you are aware, in response to a request by Dr. Moss, in August 2001 Dr. Mayr provided one vial of lyophilized tissue culture material originating from the vaccinia virus MVA as described by Mayr, et al. in 1975 (Passage history, properties and applicability of the attenuated vaccinia virus strain MVA, *Infection*, 3:6-14). In response to Dr. Moss's request for documentation about the material, Dr. Mayr provided to Dr. Moss a letter dated 12 September 2001, a copy of which is enclosed. Like the 19 September 1995 letter, also enclosed, under which Dr. Mayr supplied a sample of a 1983 passage of the same virus strain, the 12 September 2001 letter specifies no limitations on the use or distribution of the material by the NIAID.

Since you and I first discussed this subject by telephone on 19 April 2002 I have sought to obtain from you documentation to support Bavarian Nordic's assertion that NIAID's ability to use and distribute the material is somehow limited. This suggestion is reflected in your 9 April 2002 facsimile transmittal to Dr. Linda Gritz, Principal Scientist, Therion Biologics Corporation, of which Dr. Moss received a courtesy copy (enclosed), and was reinforced by you during our 19 April conversation. In our conversation you indicated that Dr. Mayr had provided the material to NIAID under a Material Transfer Agreement and, further, that Bavarian Nordic had acquired all MVA materials in possession of Dr. Mayr

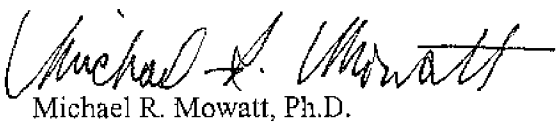
through an exclusive consulting arrangement. Your failure to supply such documentation despite my numerous requests for copies of the documentation (see my 24 April 2002, 8 May 2002 and 28 May 2002 electronic mail messages, which are enclosed) leads me to conclude that the documentation does not exist.

In summary, according to our records the NIAID received "MVA 572.FHE – 22.02.1974" from Dr. Mayr under the 12 September 2001 letter that specifies no limitations on the NIAID's use and distribution of the material or of progeny or derivatives of the material. In addition, I have found no evidence of an agreement between NIAID and Bavarian Nordic that relates to or would limit in any way the NIAID's use and distribution of the material supplied by Dr. Mayr. Accordingly, the NIAID recognizes no limitations on its ability to use and distribute the material, progeny or derivatives of the material. The Office of the General Counsel at the National Institutes of Health has reviewed this letter and the supporting documentation referenced herein and concurs with the NIAID's position.

As you know, research on and development of vaccines, including vaccines to combat HIV infection as well as smallpox and other potential agents of biological warfare, are among the very highest priorities of the NIAID. In light of the urgent worldwide public health need for such vaccines, particularly those based upon MVA, the NIAID intends to use the material supplied by Dr. Mayr for research and development projects both internally and in collaborations with organizations in the public and private sectors. In addition, the NIAID intends to distribute to qualified requestors progeny and derivatives of the material that have been and will be created by Dr. Moss and/or contractors of the NIAID in order to facilitate and expedite research and development projects that are dependent upon such materials.

Please do not hesitate to contact me should you have any questions or if I can assist you in the future.

Sincerely,



Michael R. Mowatt, Ph.D.
Director
Office of Technology Development

Enclosures (6)

cc: J. La Montagne, Deputy Director, NIAID
B. Moss, DIR, NIAID
R. Lambert, Office of the General Counsel, NIH
M. Rohrbaugh, Acting Director, Office of Technology Transfer, NIH
A. Mayr, Ludwig-Maximilians-Universität München

EXHIBIT 42

CONFIDENTIAL EXHIBIT

EXHIBIT 43

REQUEST FOR APPROVAL OF OUTSIDE ACTIVITY*

(Ref.: HHS Standards of Conduct Regulations)

☒ Initial Request ☐ Revised Request

1. NAME *(Last, First, Initial)*
MOSS, Bernard

2. ORGANIZATION LOCATION *(ICD, Office, Division)*
Laboratory of Viral Diseases, NIAID

3. TITLE OF POSITION
Chief, LVD, NIAID

4. GRADE AND SALARY *(Federal)*
06 Med Dir. $119,999

*5. NAME, ADDRESS AND BUSINESS OF PERSON OR ORGANIZATION FOR WHOM OUTSIDE SERVICES WILL BE PERFORMED
OraVax, Inc.
38 Sidney Street
Cambridge, MA 02139

6. LOCATION WHERE SERVICES WILL BE PERFORMED
38 Sidney Street
Cambridge, MA 02139

7. NATURE OF ACTIVITY (*Indicate type of activity, e.g., teaching, consultative services, and give full description of specific duties or services to be performed. Specify, when possible, the scheduled days of week and hours of day proposed activity will be performed.*)
Provide consultation on preparation of a vaccine for smallpox.

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DEPOSITION EXHIBIT
8-28-02

8. ESTIMATED TIME INVOLVED
a. PERIOD COVERED
FROM 04/21/98 TO 03/31/99

b. ESTIMATED TOTAL TIME DEVOTED TO ACTIVITY *(if on a continuing basis, give estimated time per year)*
12 days per year

c. WILL WORK BE PERFORMED ENTIRELY OUTSIDE USUAL WORKING HOURS?
☒ YES ☐ NO IF "NO, INDICATE ESTIMATED NUMBER OF HOURS OR DAYS OF ABSENCE FROM WORK

9. DO YOUR OFFICIAL DUTIES RELATE IN ANY WAY TO THE PROPOSED ACTIVITY?
☒ NO ☐ YES (Describe)

*10. IF PROVIDING CONSULTATIVE OR PROFESSIONAL SERVICES, ARE YOUR WOULD-BE ASSOCIATES RECEIVING OR WILL SEEK, A GRANT OR CONTRACT FROM A FEDERAL AGENCY? Sub-contractor for Department of Defense. Contract to make smallpox vaccine
☐ NO ☒ YES (Describe)

11. METHOD OR BASIS OF COMPENSATION
☐ FEE ☐ HONORARIUM ☐ PER DIEM ☒ PER ANNUM
☐ ROYALTY ☒ EXPENSES ☐ OTHER *(Specify)*

12. WILL COMPENSATION BE DERIVED FROM A HHS GRANT OR CONTRACT?
☒ NO ☐ YES *(Describe)*

13. THIS REQUEST IS MADE WITH FULL KNOWLEDGE OF DEPARTMENT AND OPERATING DIVISION POLICY AND PROCEDURES ON OUTSIDE ACTIVITIES. THE STATEMENTS I HAVE MADE ARE TRUE, COMPLETE TO THE BEST OF MY KNOWLEDGE AND BELIEF.

14. SIGNATURE OF EMPLOYEE
Bernard Moss

15. DATE
4/13/98

16. ADDITIONAL INFORMATION ATTACHED
☐ YES ☒ NO

17. ACTION RECOMMENDED BY REVIEWING OFFICIAL
☑ APPROVAL ☐ DISAPPROVAL
b. SIGNATURE
for
c. TITLE
Thomas J. Kindt, Ph.D.
Director, DIR, NIAID
d. DATE
4.21.98

18. ACTION TAKEN
☑ APPROVAL ☐ DISAPPROVAL
b. SIGNATURE
Roger E. Pellis
c. TITLE
Roger Pellis
Executive Officer, NIAID
d. DATE
4/21/98

INSTRUCTIONS

*Item 5 - Self-Employment: If applicable, indicate self-employment, the type of service (as medical, legal, etc.), whether alone or with partners, giving their names, and, if providing professional services to a large number of clients or patients, estimate the total number rather than listing them separately.

*Item 10 - Federal Grants or Contracts involved: Describe the Federal grants or contracts (type, granting or contracting department, etc.). Full details must be provided on any aspect of professional and consultative services which involves, directly or indirectly, the preparation of grant applications, contract proposals, program reports, and other material which are designed to become the subject of dealings between institutions and government units and the Federal Government.

*Item 16 - Attachments: Be sure to sign copies of all attachments submitted.

*ITEM 17 - COMMENTS OF REVIEWING OFFICIAL

*ITEM 18 - REASON FOR DISAPPROVAL

REQUEST FOR APPROVAL OF AN OUTSIDE ACTIVITY
SUPPLEMENTAL INFORMATION

Employee Name: Bernard Moss, M.D., Ph.D.

Position Title: Chief, Laboratory of Viral Diseases, NIAID

Organizational Location: (include ICD, division, laboratory, branch, etc.)

DHHS, NIH, NIAID, DIR, LVD

1. **Brief description of employee's official duties. In addition attach a copy of the position description or billet.**

Supervises the research of members of a laboratory consisting of 5 sections within the intramural program of NIAID. The goal of the laboratory is to conduct research on the molecular biology of viruses, virus-host interactions, the immune responses to virus infection, and new approaches to prevention and treatment of viral disease.

2. **Brief description of outside activity.**

Provide consultation on preparation of a vaccine for smallpox from April 21, 1998 through March 31, 1999 (12 days per year).

3. **Explain why the activity cannot be performed as an official duty including how it does not relate to NIH responsibilities, policies, and programs?**

Dr. Moss is responsible for directing a research laboratory, supervising junior researchers and conducting research principally on aspects of vaccinia virus transcription and the development of vaccinia virus vectors for vaccines against viral diseases. New data arising from this work is published in scientific journals or presented orally at workshops. The proposed activity is to serve as a consultant for OraVax which conveys knowledge obtained from a large segment on the scientific community as well as from the laboratory of Dr. Moss.

4. **Is the outside organization a recipient or potential recipient of any grants or contracts from the intramural program of your ICD? Is the outside organization a recipient of (or in the process of negotiating) any direct or indirect collaborative agreements or Cooperative Research and Development Agreements (CRADA) with the intramural program of your ICD? Is there any direct or indirect support of staff, guest workers, or other individuals in the intramural program of your ICD?**

A). No
B). No
C). No

5. **If consulting with a law firm, do you have any financial associations with the client (or potential**

N/A

Supplement to Form HHS-520
"Request for Approval of Outside Activity"

Instructions:

Use this supplement with Form HHS-520 for all compensated activities except writing and editing or service on boards or committees.

Complete Part A. Complete Parts B, C, D, when applicable. Submit this form with Form HHS 520.

Initiate Form HHS-520 far enough in advance of the activity so that it reaches the ICD Deputy Ethics Counselor in sufficient time for approval prior to the date of the activity.

Standards of Ethical Conduct for Employees of the Executive Branch and NIH Manual Chapter 2300-735-4 contain the rules and regulations pertaining to outside activities.

Part A - General Information

Name (Last, first, middle initial)	Organization Location	Grade and Salary
MOSS, Bernard	LVD, NIAID Bethesda, MD	06 Med Dir. $119,999
Title of Position	**Type of Activity**	
Chief, Laboratory of Viral Diseases, NIAID	☐ Teaching/Lecturing ☐ Consulting with Law Firm	
Name of Outside Organization	☒ Consulting ☐ Clinical/Private Practice	
OraVax		

Part B - Employment Agreement for Consulting

This contract relates to consulting work proposed by an Outside Employer and the Employee, identified herein as the Consultant.

The following items are agreed to by both the Outside Employer and the Consultant:

1. The proposed work will not interfere in any way with the Consultant's responsibilities at the NIH and will be performed only on non-duty time, annual leave, or leave without pay.
2. The Consultant will not disclose to the Outside Employer any information derived from work at the NIH until it has been disclosed publicly, either in a written publication or, in an oral presentation at a lecture or meeting open to the public or publicly announced.
3. Consultation will relate only to the general knowledge and expertise of the Consultant, and may be performed on an ongoing basis; however, all information concerning NIH research shall be provided on a non-exclusive basis. Any and all agreements for exclusive consultation are prohibited.
4. The Outside Employer will have no proprietary interest in any work that the Consultant has done at the NIH.
5. Notwithstanding any other provision in the agreement, the Consultant shall not be restricted from reporting an invention made by the Consultant (whether alone or jointly to the Department of Health and Human Services (HHS)) as required by Federal regulations In 45 Part 7, *nor shall the ability of HHS to ascertain its rights in such an invention.
6. The Outside Employer will not refer to the Consultant or to an affiliation with NIH in anything distributed for publicity or product promotion.
7. The number of days the Consultant will work for the Outside Employer during the period of this contract will be:
   9 days during 1998 (year) and
   12 days during 1999 (year).
8. The method of compensation of the Consultant's services and expenses will be as follows: the employee will receive a fee per Month
9. This Consulting agreement shall become effective the date of NIH approval of the Consultant's participation in this Outside Activity.

*These regulations require the reporting of any invention made by a HHS employee that bears any relation to his/her official duties, or that was made in whole or in part during working hours, or with any contribution of Government facilities, equipment, material, funds, or information or of time or services of other Government employees on official duty.

Approved by Outside Employer: Signature of Designated Official	Date
	3-31-98
Typed Name of Designated Official	**Position in Organization**
Thomas P. Monath, M.D. Vice President, Research & Medical Affairs	VP
Phone No.	**Address**
617 494 1339	38 SIDNEY ST. CAMBRIDGE, MA 02139

EXHIBIT 44

Moss 7
DEPOSITION EXHIBIT
8-29-06

ORAVAX

CONSULTING AGREEMENT

THIS CONSULTING AGREEMENT (the "Agreement), made this day of March 30, 1998 is entered into by OraVax, Inc., a Delaware corporation with its principal place of business at 38 Sidney Street, Cambridge, Massachusetts 02139 (the "Company"), and Dr. Bernard Moss residing or having a principal place of business at Laboratory of Viral Diseases, NIAID, NIH, Building 4, Room 229, 4 Center Drive, MSC 0445, Bethesda, MD 20892-0445 (the "Consultant").

INTRODUCTION

The Company desires to retain the services of the Consultant and the Consultant desires to perform certain services for the Company. In consideration of the mutual covenants and promises contained herein and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged by the parties hereto, the parties agree as follows:

1. Services. The Consultant agrees to perform the consulting, advisory and related services to and for the Company as may be reasonably requested from time to time by the Company, including, but not limited to, the evaluation of research and development opportunities for the Company in vaccinia virology, immunology, and vaccine manufacturing. The Consultant will perform such services for a minimum of twelve (12) days per year. During the Consultation Period (as defined below), the Consultant shall not engage in any activity that would constitute a conflict of interest with the Company, including any competitive employment, business, or other activity, and he shall not assist any other person or organization that competes, or intends to compete, with the Company.

2. Term. This Agreement shall commence on the date hereof and shall continue unless sooner terminated in accordance with the provisions of Section 4.

3. Compensation.

3.1 Consulting Fees. The Consultant shall submit to the Company monthly statements, in a form satisfactory to the Company, of services performed for the Company in the previous month. The Company shall pay to the Consultant consulting fees of $1,000 per month for services actually performed and invoiced within 30 days after receipt of a monthly statement.

3.2 Reimbursement of Expenses. The Company shall reimburse the Consultant for all reasonable and necessary expenses incurred or paid by the Consultant in connection with, or related to, the performance of his services under this Agreement. The Consultant shall submit to the Company itemized monthly statements, in a form satisfactory to the Company, of such expenses incurred in the previous month. The Company shall reimburse the Consultant amounts expended as provided in this Section 3.2 within 30 days after receipt of the statement showing such expenditures. Notwithstanding the foregoing, the Consultant shall not incur total expenses in excess of $500.00 per month without the prior written approval of the Company.

3.3 Benefits. The Consultant shall not be entitled to any benefits, coverages or privileges, including, without limitation, social security, unemployment, medical or pension payments, made available to employees of the Company.

4. Termination. Either party may, without prejudice to any right or remedy they may have due to any failure of the other party to perform his obligations under this Agreement, terminate the Consultation Period upon 30 days' prior written notice. In the event of such termination, the Consultant shall be entitled to payment for services performed and expenses paid or incurred prior to the effective date of termination, subject to the limitation on reimbursement of expenses set forth in Section 3.2. Such payments shall constitute full settlement of any and all claims of the Consultant of every description against the Company. Notwithstanding the foregoing, the Company may terminate the Consultation Period, effective immediately upon receipt of written notice, if the Consultant breaches or threatens to breach any provision of Section 6.

5. Cooperation. The Consultant shall use his best efforts in the performance of his obligations under this Agreement. The Company shall provide such access to its information and property as may be reasonably required in order to permit the Consultant to perform his obligations hereunder. The Consultant shall cooperate with the Company's personnel, shall not interfere with the conduct of the Company's business and shall observe all rules, regulations and security requirements of the Company concerning the safety of persons and property.

6. Proprietary Information.

6.1 Proprietary Information.

(a) The Consultant acknowledges that his relationship with the Company is one of high trust and confidence and that in the course of his service to the Company he will have access and contact with Proprietary Information. The Consultant agrees that he will not, during the Consultation Period or at any time thereafter, disclose to others, or use for his benefit or the benefit of others, any Proprietary Information.

(b) For purposes of this Agreement, Proprietary Information shall mean, by way of illustration and not limitation, all information (whether or not patentable and where or not copyrightable) owned, possessed or used by the Company, including, without limitation, any invention, product, method, technique, formula, composition, compound, project, development, plan, research data, clinical data, vendor information, customer information, apparatus, equipment, trade secret, process, research, report, technical data, know-how, computer program, software, software documentation, hardware design, technology, marketing or business plan, forecast, unpublished financial statement, budget, license, price, cost and employee list that is communicated to, learned of, developed or otherwise acquired by the Consultant in the course of his/her service as a consultant to the Company.

(c) The Consultant's obligations under this Section 6.1 shall not apply to any information that (i) is or becomes known to the general public under circumstances involving no breach by the Consultant or others of the terms of this Section 6.1, (ii) is generally disclosed to third parties, or (iii) is approved for release by written authorization of the Board of Directors of the Company.

(d) Upon termination of this Agreement or at any other time upon request by the Company, the Consultant shall promptly deliver to the Company all records, files, memoranda, notes, designs, data, reports, price lists, customer lists, drawings, plans, computer programs, software documentation, sketches, laboratory and research notebooks and other documents (and all copies or reproductions of such materials) relating to the business of the Company.

(e) The Consultant represents that his retention as a consultant with the Company and his performance under this Agreement does not, and shall not, breach any agreement that obligates him to keep in confidence any trade secrets or confidential or proprietary information of his or of any other party or to refrain from competing, directly or indirectly, with the business of any other party. The Consultant shall not disclose to the Company any trade secrets or confidential or proprietary information of any other party.

(f) The Consultant acknowledges that the Company from time to time may have agreements with other persons or with the United States Government, or agencies thereof, that impose obligations or restrictions on the Company regarding inventions made during the course of work under such agreements or regarding the confidential nature of such work. The Consultant agrees to be bound by all such obligations and restrictions that are known to him and to take all action necessary to discharge the obligations of the Company under such agreements.

6.2 Remedies. The Consultant acknowledges that any breach of the provisions of this Section 6 shall result in serious and irreparable injury to the Company for which the Company cannot be adequately compensated by monetary damages alone. The Consultant agrees, therefore, that, in addition to any other remedy it may have, the Company shall be entitled to enforce the specific performance of this Agreement by the Consultant and to seek both temporary and permanent injunctive relief (to the extent permitted by law) without the necessity of proving actual damages.

7. Independent Contractor Status. The Consultant shall perform all services under this Agreement as an "independent contractor" and not as an employee or agent of the Company. The Consultant is not authorized to assume or create any obligation or responsibility, express or implied, on behalf of, or in the name of, the Company or to bind the Company in any manner.

8. Notices. All notices required or permitted under this Agreement shall be in writing and shall be deemed effective upon personal delivery or on deposit at an overnight mail carrier, postage prepaid, addressed to the other party at the address shown above, or at such other address or addresses as either party shall designate to the other in accordance with this Section 8.

9. Pronouns. Whenever the context may require, any pronouns used in this Agreement shall include the corresponding masculine, feminine or neuter forms, and the singular forms of nouns and pronouns shall include the plural, and vice versa.

10. Entire Agreement. This Agreement constitutes the entire agreement between the parties and supersedes all prior agreements and understandings, whether written or oral, relating to the subject matter of this Agreement.

11. Amendment. This Agreement may be amended or modified only by a written instrument executed by both the Company and the Consultant.

12. Governing Law. This Agreement shall be construed, interpreted and enforced in accordance with the laws of the Commonwealth of Massachusetts.

13. Successors and Assigns. This Agreement shall be binding upon, and inure to the benefit of, both parties and their respective successors and assigns, including any corporation with which, or into which, the Company may be merged or which may succeed to its assets or business, provided, however, that the obligations of the Consultant are personal and shall not be assigned by him.

14. Miscellaneous.

14.1 No delay or omission by the Company in exercising any right under this agreement shall operate as a waiver of that or any other right. A waiver or consent given by the Company on any one occasion shall be effective only in that instance and shall not be construed as a bar or waiver of any right on any other occasion.

14.2 The captions of the sections of this Agreement are for convenience of reference only and in no way define, limit or affect the scope or substance of any section of this Agreement.

14.3 In the event that any provision of this Agreement shall be invalid, illegal or otherwise unenforceable, the validity, legality and enforceability of the remaining provisions shall in no way be affected or impaired thereby.

IN WITNESS WHEREOF, the parties hereto have executed this Agreement as of the day and year set forth above.

ORAVAX, INC.

By: _____
Dr. Thomas P. Monath

Title: Vice President
Research and Medical Affairs

Date: 3/30/98

By: _____
Dr. Bernard Moss

Title: _____

Date: _____

EXHIBIT 45

CONFIDENTIAL EXHIBIT

EXHIBIT 46

CONFIDENTIAL EXHIBIT

EXHIBIT 47

CONFIDENTIAL EXHIBIT

EXHIBIT 48

OMB No. 0990-0115

Electronic Request for Proposal
SECTION A – SOLICITATION/CONTRACT FORM

OFFERORS ARE RESPONSIBLE FOR ROUTINELY CHECKING THE CMB WEBSITE http://www.niaid.nih.gov/contract/default.htm FOR ANY POSSIBLE SOLICITATION AMENDMENTS THAT MAY BE ISSUED. NO ADDITIONAL NOTIFICATION OF ANY AMENDMENTS WILL BE PROVIDED BY THIS OFFICE.

Purchase Authority: Public Law 92-218, as amended.
NOTE: The issuance of this solicitation does not commit the government to an award.

RFP Number:	Just In Time:	Small Bus. Set-Aside	[ ]Yes [X]No	Level of Effort:
		8(a) Set-Aside	[ ]Yes [X]No	[ ] Yes [X] No
NIH-NIAID-DMID-03-44	[ ] Yes	NAICS Code	541710	Total Effort:
	[X] No	Size Standard	500 employees	[N/A]

TITLE:
Development and Testing of a Modified Vaccinia Ankara (MVA) Vaccine

Issue Date: August 15, 2002	Due Date: September 30, 2002 Time: 4:00 PM, EST	Technical Proposal Page Limits: [ ] Yes *(see "How to Prepare and Submit Electronic Proposals")* [X] No

ISSUED BY:

Jacqueline C. Holden
Contracting Officer
Contract Management Branch, DEA
NIH, NIAID
6700-B Rockledge Drive
Room 2230, MSC 7612
Bethesda, MD 20892-7612

[ ] ***We reserve the right to make awards without discussion.***

NO. OF AWARDS:

[ ] Only 1 Award
[X] Multiple Awards

PERIOD OF PERFORMANCE:

Part A: 3 years beginning on or about 01/31/2003
Part B, Option: Up to 24 Months

Offers will be valid for 120 days unless a different period is specified by the Offeror on the form entitled "Proposal Summary and Data Record, NIH-2043" (See SECTION J - Attachments)

The Official Point of Receipt for the purpose of determining timely delivery is the Contract Management Branch as stated above. The paper copy with original signatures is the official copy for recording timely receipt. If the paper copy of your proposal is not received by the Contracting Officer or Designee at the place and time specified, then it will be considered late and handled in accordance with HHSAR 352.215-70 entitled "Late Proposals and Revisions" located in this Solicitation. FACSIMILE SUBMISSION OF PROPOSALS IS NOT ACCEPTABLE.

POINT OF CONTACT **– Phil Hastings** ***--COLLECT CALLS WILL NOT BE ACCEPTED--***

Telephone: Direct 301-496-0194 *Main* 301-496-0612	*Fax* 301-402-0972	*E-Mail* ph23k@nih.gov

Updated thru FAC 2001-07 (05/15/02)

CANNON
7

TABLE OF CONTENTS

PLEASE NOTE: If you intend to submit a proposal in response to this RFP, you are requested to submit a **PROPOSAL INTENT RESPONSE SHEET** by **Monday, September 9, 2002.** Your expression of intent is not binding but will greatly assist us in planning for proposal evaluation.

BACKGROUND / STATEMENT OF WORK / NOTES TO OFFERORS
Background

Development and Testing of a Modified Vaccinia Ankara (MVA) Vaccine
RFP NIH-NIAID-DMID-03-44

The National Institute of Allergy and Infectious Diseases (NIAID) is the primary institute at the National Institutes of Health (NIH) for emerging infectious disease research, including research on pathogens that can be used as agents of bioterrorism. Bioterrorism is defined as the use of microorganisms that cause human disease, or the toxins released from them, to harm people or elicit widespread fear or intimidation of society.

The events of the past year have significantly changed the world's perception of the nature and degree of the threats posed by the use of infectious agents as weapons of bioterrorism. The risk of using such weapons once appeared to be restricted to military encounters. However, the deliberate exposure of postal workers, other government employees and the American public at large to *Bacillus anthracis* spores highlighted the need to devise appropriate and effective measures to protect all U.S. citizens from the harmful effects of those biologic agents of most concern.

Smallpox is an infectious disease caused by the variola virus, a member of the orthopox family. The global eradication of smallpox in 1980 has been heralded as one of the most significant feats of mankind. In 1971, the last case of smallpox in the Americas was seen. Shortly thereafter, routine smallpox immunization was discontinued in the U.S. because the risk of vaccination outweighed the threat of the disease. Recent knowledge on the weaponization and availability of smallpox stocks to rogue nations has increased concern about the population's vulnerability to this disease. As a result of this assessment, the U.S. government is currently procuring enough smallpox vaccine for every U.S. citizen.

The vaccine that contributed to the eradication of smallpox was based on a live, replicating vaccinia virus that had been attenuated over time through serial passages in tissue culture. This vaccine is reactogenic, causing common side effects such as redness and swelling at the site of vaccination, fever, or muscle aches in over 90% of people. Although rare in healthy recipients of the vaccine, vaccination with vaccinia can cause encephalitis, eczema vaccinatum, disseminated vaccinia and even death. The frequency of these events is increased as the ability to control the vaccinia replication is decreased such as when a person's immune system becomes increasingly compromised. The number of U.S. citizens at risk for these rare events has increased over the years due to life-saving drugs and medical procedures which compromise the immune system such as those drugs administered following organ transplant and the increased number of cases of HIV-infection. This fact has raised concerns about the wisdom of vaccinating every U.S. citizen with live, replicating vaccinia vaccine, should that need arise.

Modified Vaccinia Ankara (MVA) is a strain of vaccinia that has been further attenuated by serial passage in chick embryo fibroblasts. MVA has a substantial clinical history due to its extensive use as a vaccine to immunize over 120,000 people during the smallpox mass vaccination campaign in Germany in the 1970's. In most human and primate cells, replication of the virus is blocked at the final stages of maturation, but most of the viral proteins are produced. Very limited replication (less than two plaque forming unit/cell) is seen in some mammalian cell lines. The gene deletions (approximately 33kbp) associated with MVA have been partially characterized. At least two host range genes are absent, as are the genes associated with at least four immunomodulatory proteins. Both neutralizing and hemagglutination inhibition antibodies are, however, produced. There is also some evidence that MVA can protect against variola virus challenge in monkeys. Most recently tested as an experimental vaccine vector for the delivery of other vaccine candidates, including HIV and cancer vaccines, the safety profile has been expanded to include contemporary data in recipients with potential immunocompromised status.

To address the urgent and compelling need to accelerate the development and stockpiling of MVA smallpox vaccines, the government has developed a comprehensive approach that includes both collaborative opportunities with NIAID as well as contract awards. Collaborative opportunities are <u>not</u> the subject of this Request for Proposals (RFP), however it is briefly described here for the sake of completeness. Collaborative opportunities from NIAID are available to all legitimate parties and include: the availability of a master seed stock of MVA from NIAID; the availability of some characterized reagents and standard operating procedures (SOPs) for immunologic measurements; assistance in evaluating Investigational New Drug (IND) grade vaccine candidates in relevant animal models; and assistance with testing of IND vaccine candidates in clinical trials through the NIAID clinical trials contract network. Further information regarding the requirements for requesting collaborative opportunities is described below.

It is the intent of the Government to provide contract support for the development and stockpiling of MVA vaccines through the issuance of three sequential Request for Proposals (RFPs). The first procurement action and the subject of this RFP (NIAID-DMID-03-44) is intended to provide resources for the initial development of MVA vaccine candidates. In addition, the Government intends to issue a second RFP during the summer of 2003, entitled "Production and Acquisition of MVA Vaccine." The objective of the second RFP will be to manufacture, formulate, fill and finish, and test, in accordance with cGMP regulations, up to 30 million doses of MVA vaccine to constitute the U.S. Government's stockpile for emergency use under IND, and to provide a licensure plan to include the conduct of expanded human safety studies required for licensure and the conduct of pivotal animal protection studies. A third contract action for the acquisition of a licensed product is being planned for 2005, under the auspices of the Centers for Disease Control (CDC).

Participation in NIAID's initial RFP (NIAID-DMID 03-44) will not be a pre-requisite for participation in subsequent MVA vaccine procurements planned by the NIAID and the CDC.

Information Required to Request
Consideration for NIAID Collaborative Opportunities

1. Evidence that the offeror/requestor/interested party has secured access to all intellectual property, know-how and tangible materials for this proposed work, or has a plan to secure such intellectual property, know-how and tangible materials.

2. Characterization data for the vaccine candidate that demonstrates manufacturing, control and safety features. Data should include, but not be limited to, the following:

    a. Chemistry, manufacturing and control testing information to include:

        i. Documentation of all raw materials used in the production of the master and working seed viruses and any cell substrates used in the production of the vaccine. All animal derived materials used in the production of the master seeds or cell banks as well as the manufacturing of the vaccine should be described and the country of origin of the animals should also be provided. Tabular form is requested.

        ii. Description of the production of the seed virus and cell banks used in vaccine production. Inclusion of a flow diagram is requested.

3. Description of vaccine production. Inclusion of a flow diagram is requested.

4. Summary of all process and release testing and the respective data to assess purity, potency, and safety of the product.

5. Data to support the stability and consistency of manufacturing. Examples of the type of stability for MVA includes demonstration of the stability of the genotype and phenotype and inclusion of a complete evaluation of the non-replicative/or limited replication of the vaccine candidate in multiple mammalian cell lines.

6. Pre-clinical safety data to include:

    a. Data demonstrating the safety of the candidate vaccine as well as the design of the preclinical studies used in the assessment.

    b. Data to support the lack of/or limited replication in animals and the stability of the genetic phenotype.

7. Documentation that the vaccine candidate can elicit an immune response in animals. Rationale for the choice of the animal model used and the regimen evaluated should also be included.

8. All animal data evaluating vaccine dosage and immunization regimens.

9. Any additional pre-clinical data to demonstrate "proof of concept", effectiveness. Protocols should also be included.

For more information regarding collaborative opportunities with NIAID, please contact Deborah Katz of the Office of Biodefense Research Affairs, DMID/NIAID, at dkatz@niaid.nih.gov.

Statement of Work – PART A
Development and Testing of a Modified Vaccinia Ankara (MVA) Vaccine
RFP NIH-NIAID-DMID-03-44

Introduction

This RFP (NIH-NIAID-DMID-03-44), for the initial development of MVA vaccine candidates, consists of 2 parts. Part A addresses development, manufacturing, testing and the conduct of Phase I studies in healthy populations. Specifically, the main objectives of Part A are to:

- Develop an MVA vaccine. This will include the development of the product as well as preparation of the chemistry, manufacturing and control (CMC) data to support use of this product under an IND application submitted to the Food and Drug Administration (FDA).
- Assess protection and immunogenicity provided by MVA vaccines in appropriate animal models.
- Conduct Phase I clinical trials to assess the safety and immunogenicity of MVA candidate vaccines.
- Develop a feasibility plan to manufacture and fill at least 30 million doses of MVA vaccine under current Good Manufacturing Processes (cGMP). This plan will include product characterization and product release and stability testing. The plan will also include production and testing of diluents, preservatives and other final ingredients that may be required.

Part B is an option to this contract requirement and, if exercised by the Government, will provide for the conduct of expanded Phase II clinical studies in healthy populations (i.e., adults and children) and Phase I and II studies in "at risk" (i.e., immunocompromised) populations.

Offerors must submit proposals for both Part A and Part B. For Part A, multiple awards may be made. For the Part B option, if exercised, the Government will select the candidate vaccine(s) that meet the milestones outlined in the Statement of Work and show the best potential of being a successful MVA vaccine candidate. Contract(s) awarded under this RFP will be milestone and product driven. Therefore, following each milestone and the subsequent review by NIAID staff, down-selection (i.e., discontinuation of contract support by means of early contract termination) may occur based on the quality of products, results of pre-clinical testing, or if Statement of Work milestones are not met.

The U.S. Government has determined that the urgent nature of the current threat requires an accelerated pace of development, testing, approval and procurement of an emergency stockpile of this vaccine. Although future smallpox vaccines may be derived from other strains, formulated in a different manner, or based on another platform these novel approaches are not being considered for this solicitation due to the urgent need.

Statement of Work – Part A

Independently, and not as an agent of the government, the Contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities not otherwise provided by the Government as needed to perform the work described below.

This procurement will be milestone-driven and awarded in phases. Periodic assessments of progress and continuation of subsequent milestones will be based on timeliness and quality of deliverables and consultations between the contractor and NIAID program staff. **Cost proposals must be prepared based on the estimated cost of each milestone.**

A. Using technology known to be acceptable in the production of vaccines licensed for use in the U.S., develop a prototype MVA vaccine that will protect against challenge in relevant animal models.

1. Milestone 1: Within three months of award, produce a bulk pilot lot (to support at least 5000 clinical doses) of prototype MVA vaccine, in a formulation that represents the process to be scaled up for subsequent large-scale production. This lot of vaccine is to be produced under manufacturing conditions necessary to support the use of this product under IND and future large-scale manufacturing. ***(See Note #1 to Offeror.)***

2. Milestone 2: Within six months of award of Part A, provide the NIH with 5000 doses of the final vaccine prototype, filled, finished and released as single dose vials and all information and authorization necessary to enable the government to file an IND for Phase I clinical trials, excluding only that considered to be proprietary, which may be summarized for NIAID and submitted to the FDA in a separate master file. ***(See Note #2 to Offeror.)***

3. Milestone 3: Within six months of award, assess the protection and immunogenicity provided by MVA vaccine prototypes in appropriate animal models according to protocols approved by NIAID. ***(See Note #3 to Offeror.)***

4. Milestone 4: Within 6 months of award, develop and submit for review and approval to NIAID, a clinical development plan for the evaluation of the vaccine, including protocols for the conduct of Phase I clinical trials (Part A), including the core Phase I requirements described in Attachment I, and protocols for the conduct of Part B optional clinical trials. To facilitate comparison of immunological and safety data currently being derived from ongoing studies of vaccinia, the NIAID will oversee the development of standardized Phase I (Part A) and Part B protocols in order to achieve consensus from all collaborating and participating parties.

   For clinical trials conducted by the contractor under their own IND, the plan must provide information about the contract research organization (CRO) proposed to conduct the trials, including information about clinical personnel, laboratory procedures, proposed sites and timelines for their completion. The plan should describe the operational procedures the company will follow to assure adequate oversight of clinical trials, timely and accurate reporting of information to the FDA, structure and responsibilities of a data and safety monitoring board, as well as policies of how data will be processed, shared and published. The plan should specify how NIAID would be kept apprised of progress and communications with the FDA, including processes to assure NIAID may co-monitor or provide for independent audit of the clinical trial.

   The Government, acting through the NIH, will facilitate attaining necessary resources to ensure that immunological assays from samples obtained in Phase I and Part B trials are evaluated using standardized assays that are currently being characterized and validated.

5. Milestone 5: Upon NIAID approval of the Phase I protocol, the contractor shall initiate Phase I trials. Standardized protocols, central laboratories and characterized reagents shall be used for neutralization and ELISA assays in all human trials.

6. Milestone 6: Within 12 months of the award, provide a feasibility plan to manufacture, formulate, fill and finish, test, and deliver to the Government up to 30 million doses of the candidate MVA vaccine suitable for storage in a stockpile for emergency use. The plan should include proposed steps to be taken to monitor the quality (e.g., stability testing plan) and to replenish the stockpile as needed to maintain its ready availability for emergency use under IND, as well as address the product development path for licensure. Accordingly, manufacturing plans should be designed for manufacture of licensed vaccine, not for retention of the vaccine in an IND status.

   The feasibility plan shall include:

   a. Details of the process to scale-up production, including data to support the approach, i.e., documentation of successful scale-up of similar product class or data from intermediate scales of production;

   b. Timeline for production and delivery of up to 30 million doses of product;

   c. Strategy that will be pursued to seek a U.S. license for the product and to provide continued support for maintaining an active Government-held IND; to include obtaining expanded safety and immunogenicity data in all populations and the plan to meet the requirements of the Animal Efficacy Rule;

   d. Estimate of the cost/dose of up to 30 million doses delivered to the Government for use; and

   e. Plan to monitor (stability testing) and replenish the stockpile as needed in consultation with the managers of the Government stockpile. ***(See Note #4 to Offeror.)***

7. Milestone 7: Within 15 months of award, complete an interim clinical trial report that includes data summary, data analysis and interpretation and conclusions for the Phase I trial. These data may be used by the Government and/or the contractor for consultations with the FDA concerning planning for subsequent product development and clinical trials.

8. Milestone 8: Within 30 months of award, complete Phase I clinical trials and provide a report that captures all Phase I clinical trial follow-up and duration of immunity data. The report will include data summary, analysis and interpretation as well as final conclusions and recommendations.

B. Meetings and Conferences - The Contractor shall participate in regular meetings to coordinate and direct the contract efforts as directed by the NIAID Project Officer. Such meetings may include, but are not limited to, meetings of all contractors to discuss clinical protocol design; meetings with individual contractors and other PHS officials to discuss technical, regulatory and ethical aspects of the program, and meetings with NIH technical consultants to discuss down-selection criteria and technical data provided by the contractor. ***(See Note #5 to Offeror.)***

[END OF STATEMENT OF WORK – PART A]

EXHIBIT 49

CONFIDENTIAL EXHIBIT

CERTIFICATE OF SERVICE

I hereby certify that on January 10, 2007, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF which will send electronic notification of such filing to the following:

John W. Shaw, Esquire
YOUNG CONAWAY STARGATT & TAYLOR LLP
The Brandywine Building, 17th Floor
1000 West Street
Wilmington, DE 19801

Additionally, I hereby certify that true and correct copies of the foregoing were caused to be served on January 10, 2007 upon the following individuals in the manner indicated:

BY E-MAIL AND HAND DELIVERY

John W. Shaw, Esquire
YOUNG CONAWAY STARGATT & TAYLOR LLP
The Brandywine Building, 17th Floor
1000 West Street
Wilmington, DE 19801

BY E-MAIL
(AND FEDERAL EXPRESS on 01/11/07)

Edward A. Pennington
BINGHAM MCCUTCHEN LLP
3000 K Street, Suite 300
Washington, DC 20007

/s/ James W. Parrett, Jr.

James W. Parrett, Jr. (#4292)